NIH Plan to Implement Recommendations of the
NIH AIDS Research Program Evaluation Task Force

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Prepared by the

National Institutes of Health

in response to the

Report of the NIH AIDS Research Program Evaluation Task Force

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Preface

It is my pleasure to present the NIH Plan to Implement Recommendations of the NIH AIDS Research Program Evaluation Task Force. This plan is the result of a collaborative effort by the National Institutes of Health (NIH), including the Office of AIDS Research (OAR) and all of the NIH Institutes and Centers, to meet the vision and goals of the experts who reviewed the NIH AIDS research program.

In late 1994, it became clear that AIDS research had reached a turning point, and new priorities and new directions for the future were necessary. A unique process was initiated: The NIH AIDS Research Program Evaluation Task Force, a panel of more than 100 distinguished scientists and experts from the United States and around the world, chaired by Dr. Arnold Levine of Princeton University, was formed by the Office of AIDS Research Advisory Council. The Task Force was asked to conduct a comprehensive evaluation of the entire NIH AIDS research program. This review was unprecedented because of the magnitude of the AIDS research program, which cuts across every NIH Institute and Center. The group was asked to assess whether the program as a whole was moving effectively and efficiently toward the goal of preventing and curing AIDS.

Six Area Review Panels reviewed AIDS research in the following areas: Etiology and Pathogenesis; Drug Discovery; Clinical Trials; Vaccine Research and Development; Behavioral, Social Science, and Prevention Research; and Natural History, Epidemiology, and Prevention Research. *Ad hoc* groups examined opportunistic infections, animal models, alternative and complementary therapies, training programs, and AIDS research centers. The entire Report of the NIH AIDS Research Program Evaluation Task Force, commonly known as the "Levine Report," is available on the OAR World Wide Web site of the Internet at http://www.nih.gov/od/oar/oar_home.htm.

This landmark report assessed all NIH-sponsored AIDS research to determine whether the most promising areas of science were being supported, the critical scientific questions were being addressed, and the most effective use was being made of Federal AIDS research resources. It provided a blueprint for restructuring the NIH AIDS research program to streamline research, strengthen high-quality programs, eliminate inadequate programs, and ensure that the American people reap the full benefits of their substantial investment in AIDS research.

Most importantly, that blueprint is becoming a reality. The report has had a significant effect on almost every aspect of the AIDS research program—in setting the scientific agenda, refocusing priorities, and shaping the AIDS research budget.

The recommendations helped frame the OAR's final distribution of the FY 1997 appropriation, the FY 1998 research plan and budget request, and the FY 1999 research plan. We believe that the priorities established by these recommendations will have an impact not only on Government-supported research but on the research agendas of industry and private research organizations both in the United States and abroad.

I would like to briefly highlight some of the most significant actions we have taken as a result of this important process. The report has had a profound impact in helping to establish the appropriate balance in the AIDS research program in two critical areas: (1) between investigator-initiated research grants and targeted, directed science and (2) between research to develop treatments and an eventual cure for those who are already infected and research to prevent infection.

Before embarking on the evaluation process, OAR already had identified the need to place greater emphasis on investigator-initiated science and to increase the proportion of funding devoted to basic research. The Levine Report confirmed these priorities. Between FY 1994 and the FY 1998 President's budget request, OAR has increased the number of research grants by 50 percent, thus encouraging innovation from a wider group of investigators.

Perhaps the most significant recommendations of the report relate to vaccine research. The changes that have been implemented in this area have enormous potential significance, not only for AIDS but for other diseases as well. The report recognized that only a truly effective preventive vaccine can limit and eventually eliminate the threat of AIDS. The reviewers placed high priority on the need to restructure and reinvigorate the AIDS vaccine program, with leadership and guidance from eminent non-Government scientists.

NIH has taken a number of steps to carry out this critical recommendation. Nobel laureate Dr. David Baltimore was recruited to lead this reinvigorated effort, and he has assembled a group of outstanding scientists to serve with him on the AIDS Vaccine Research Committee. Their charge is to energize the development of new strategies toward the discovery and development of a safe and effective AIDS vaccine. To facilitate this effort, OAR has made a major financial investment in AIDS vaccine research. The FY 1998 budget request represents a 33.6-percent increase for vaccine research in the 2-year period since FY 1996, a sign of our commitment to this effort. The President also emphasized the importance of AIDS vaccine research both in his State of the Union address and in a commencement speech in May 1997 at Morgan State University. At that time he also announced another important NIH vaccine initiative, the establishment of a joint National

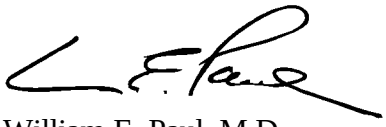
Institute of Allergy and Infectious Diseases/National Cancer Institute (NIAID/NCI) intramural vaccine research center. Progress made in the development of an AIDS vaccine will certainly have implications for vaccines against other life-threatening illnesses.

The Levine Report also urged NIH to develop a Prevention Science Agenda, combining behavioral research and biomedical interventions such as topical microbicides, female-controlled barriers, methods to prevent mother-to-child transmission, and prevention and treatment of sexually transmitted diseases. OAR convened a group of experts to assist us in identifying the most promising areas for additional investment, and we have transferred funds to the Institutes for these initiatives.

The balance between research to develop treatments for those who are infected and research to develop vaccines and other prevention methods for those who are at risk is a delicate one and will almost certainly shift as science progresses.

NIH approached the implementation of the recommendations with seriousness of purpose, involving the Director of NIH, the Directors of each of the Institutes and Centers, scientific and program staff across NIH, and the OAR Advisory Council. To each of them, I express my sincere thanks and gratitude for their time, contributions, and willingness to look for new solutions.

The Nation has invested major resources in the NIH AIDS research program. I believe that the steps taken by OAR over the past few years, resulting in this plan, have allowed us to demonstrate that the Nation's investment is indeed well spent. The process involved an intensive outside evaluation of the NIH by hundreds of scientific experts and community representatives and a deliberative and comprehensive implementation of their recommendations. Because of the legislative authorities provided to OAR for planning and budgeting for AIDS research, it has been possible to set new scientific priorities and to reshape and restructure the research enterprise toward our goal of preventing and curing AIDS.



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August 1997

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Introduction

Introduction

The National Institutes of Health (NIH) has developed the NIH Plan to Implement Recommendations of the NIH AIDS Research Program Evaluation Task Force to respond to the 1996 Evaluation Task Force Report and to reinvigorate the NIH HIV/AIDS research program. As recommended, the Office of AIDS Research (OAR) has worked with the NIH Institutes, Centers, and Divisions (ICDs) to develop this plan, and all the relevant ICD Directors, as well as the Director of NIH, have reviewed and approved it prior to its endorsement by the OAR Advisory Council (OARAC) in March 1997. The plan provides a comprehensive report on the changes and new programs initiated by the ICDs to further strengthen the NIH AIDS research effort. Through these efforts, NIH is renewing its commitment to address the current and emerging scientific priorities and opportunities for ending the devastation caused by AIDS.

The priorities and insights highlighted in the NIH AIDS Research Program Evaluation Task Force Report also have been incorporated into the annual planning process. The OAR Coordinating Committees utilized both the Task Force report and this plan in developing the FY 1999 NIH Plan for HIV-Related Research, which outlines the direction and priorities for NIH in its future efforts.

The NIH AIDS Research Program Evaluation Task Force

In late 1994, the OAR AIDS Program Advisory Committee, subsequently replaced by OARAC, formed the NIH AIDS Research Program Evaluation Task Force to evaluate all NIH-sponsored AIDS research and help set future research priorities. The Task Force consisted of a Working Group and six Area Review Panels that focused on the major areas of AIDS research: (1) Etiology and Pathogenesis; (2) Drug Discovery; (3) Clinical Trials; (4) Vaccine Research and Development; (5) Behavioral, Social Sciences, and Prevention Research; and (6) Natural History, Epidemiology, and Prevention Research. Subpanels also were formed to evaluate NIH activities in the areas of Opportunistic Infections (OIs) and Complementary and Alternative Medicine (CAM). More than 100 scientists from academia and industry as well as representatives from community constituency groups participated in these panels and subpanels.

Task Force members reviewed budget and program information provided by the 24 ICDs that sponsor AIDS research as well as information available from databases maintained by OAR and the Division of Research Grants (DRG). Members also conducted interviews with ICD Directors, key program staff, intramural and extramural scientists, and a wide variety of experts from inside and outside the field of AIDS research. In performing their review, Task Force members were asked to take a broad view of the NIH AIDS research programs, assessing how the various research components fit together and determining whether the program is effectively and efficiently moving toward the goal of preventing, treating, and curing HIV infection and AIDS.

After review by OARAC, the Working Group report and Area Review Panel reports were accepted and released in March and July 1996, respectively. The individual Area Review Panel reports document their specific evaluations and detailed recommendations. The Working Group took a broader view, identifying key issues and developing major recommendations that span scientific areas and underpin the overall NIH AIDS effort. In some cases, the Working Group

report reflects a consensus position that reconciles somewhat divergent conclusions found in individual Area Review Panel reports.

Overall, the Task Force report provides a blueprint for restructuring the NIH AIDS research program to streamline AIDS research, strengthen high-quality programs, eliminate inadequate programs and projects, and ensure that the American people reap the full benefits of their substantial investment in AIDS research. The Task Force report contains more than 400 recommendations addressing specific programs or projects and ICD initiatives contained in the NIH AIDS research portfolio.

Development of the Implementation Plan

Immediately after the release of the Working Group report, the NIH Director and Associate Director for AIDS Research began meeting with key ICD Directors to discuss and respond to crucial recommendations contained in the report. Many proposed changes were immediately implemented.

OAR then began working with the ICDs to develop a formal implementation plan to respond to the Working Group and Area Review Panel recommendations not previously addressed. To this end, the recommendations were divided into three general categories: ICD-specific, OAR-specific, and cross-ICD. Recommendations concerning programs/projects supported by a specific Institute or Center were assigned to the individual ICD to develop a response. Those recommendations related to specific activities supported by OAR were assigned to that office. Finally, recommendations that applied to efforts supported by multiple ICDs were assigned to Implementation Groups that were specifically established to develop coordinated responses. A total of seven Implementation Groups were established with appropriate representatives from the ICDs having research portfolios in the following areas: Etiology and Pathogenesis; Drug Discovery; Clinical Trials; Vaccines; Prevention (encompassing Natural History and Epidemiology and Behavioral and Social Sciences research); Primate Centers; and Databases and Repositories.

From March through December 1996, the ICDs, OAR, and the Implementation Groups developed draft responses to each Task Force recommendation. In late December, the draft document was given to all of the ICDs for review to ensure that it reflected the NIH current and planned efforts to implement or address the recommendations. The NIH Director and ICD Directors then reviewed a revised draft of the plan in January/February, and the penultimate document was discussed at the March 14 meeting of OARAC.

Format of Responses to Recommendations

The response to each recommendation is divided into two major sections: “Current Status” and “Future Actions.” The Current Status section describes ongoing NIH activities targeted to the recommendation since the release of the Task Force report. The Future Action section outlines any additional activities planned by NIH in response to the recommendation. In some cases, specific time lines for planned efforts are presented.

The responses provide a comprehensive overview of NIH-supported activities in addressing the key issue/concern in each recommendation but do not provide a detailed account of every effort. As the different Task Force reports occasionally presented similar or identical recommendations, responses to

these have been consolidated under the most prominent recommendation, and referral notes have been placed where appropriate. Additional referral notes are provided in cases where portions of two or more responses overlap.

Summary of Responses to the 14 Major Working Group Recommendations

NIH has implemented many of the Working Group recommendations. The following is a summary of the activities and plans that have been implemented in response to the 14 major Task Force recommendations.

1. Increase support and improve peer review of investigator-initiated research

The percentage of investigator-initiated project grants for HIV/AIDS research has dramatically increased from 23 percent in fiscal year (FY) 1994 to an estimated 52 percent in FY 1998. NIH has decreased its use of targeted initiatives such as Requests for Applications (RFAs). At the same time, NIH has placed increased value on investigator-initiated AIDS research, and the maturity of the science has permitted the development of more sophisticated and fundable research applications. As a result, many of the new grants awarded support cutting-edge research on basic human immunology.

DRG, OAR, and the ICDs have begun to work together more closely to improve communication and encourage mutual awareness on AIDS-related issues and research priorities. DRG will continue to seek high-caliber scientific reviewers for the Initial Review Groups (IRGs) and will work closely with ICD staff and professional societies to ensure that researchers with the appropriate scientific expertise participate on study sections. To encourage further communication and dissemination of AIDS research priorities between DRG and ICDs, DRG Scientific Review Administrators (SRAs) participated in the FY 1999 OAR Coordinating Committees and in the development of the FY 1999 NIH Plan for HIV-Related Research.

NIH will continue to use various programs and mechanisms to ensure training and support for new investigators in AIDS research. OAR has established a Coordinating Committee on Training and Infrastructure that developed specific objectives and strategies and set priorities in the FY 1998 and FY 1999 NIH Plan for HIV-Related Research.

2. Establish a restructured trans-NIH vaccine research effort

As recommended by the Working Group, a nongovernmental advisory committee has been established, and NIH has enlisted as chair a highly esteemed Nobel laureate, Dr. David Baltimore. Dr. Baltimore and the AIDS Vaccine Research Committee (AVRC), which was established under OARAC, will provide advice and guidance to the NIH AIDS vaccine research efforts. OAR also has given the National Institute of Allergy and Infectious Diseases (NIAID) an additional $6 million in FY 1997 funds for new AIDS vaccine programs and $1 million to the AVRC to support special AIDS vaccine initiatives. NIAID has recently released a Program Announcement (PA) to support a reinvigorated research effort in this field. The NIH AIDS FY 1998 budget request includes a 33.6-percent increase over the FY 1996 level of funds for AIDS vaccine research efforts.

In June 1996, NIAID and OAR convened a multidisciplinary panel of experts to conduct a review of the NIAID HIV Vaccine Efficacy Trials Network (HIVNET) organization, governance, research, and funding. The review was released in September 1996. The Panel recommended that HIVNET be continued and given the priority to establish the capacity for the prompt and scientifically sound assessment of vaccine efficacy both domestically and internationally. It was recommended that HIVNET continue a strong multidisciplinary approach to maintain or develop its capacity for evaluating both vaccine and nonvaccine interventions. The HIVNET cohorts were recognized as a valuable resource for evaluating other biomedical and behavioral interventions for preventing sexual, parenteral, and perinatal transmission of HIV.

3. *Augment research efforts to better understand the human immune system*

Many of the new grants funded since 1994 focus on this important area of research. OAR, in collaboration with the relevant ICDs, will convene a series of workshops to address the specific scientific needs highlighted by the Task Force report. The scientific goals inherent in this recommendation have been incorporated into the FY 1998 and FY 1999 NIH Plan for HIV-Related Research.

4. *Develop a comprehensive NIH HIV prevention science agenda*

The Prevention Sciences Working Group (PSWG) has been established under the auspices of OARAC; it is chaired by Dr. James Curran. The PSWG has met several times and has already identified a series of scientific priorities targeting specific areas of prevention science research, including behavioral and social science research as well as natural history and epidemiology investigations. These priorities were taken into account in the distribution of $6 million to the ICDs from the FY 1997 OAR Prevention Science Initiative Fund.

5. *Integrate all adult clinical trial programs into a single network*

OAR and NIAID Directors cochair a panel of representatives from the involved ICDs and investigator groups that will develop a proposal to improve the efficiency, scientific productivity, and public health relevance of the NIH-sponsored adult clinical trials network. A draft proposal will be developed and submitted to the Directors and Advisory Councils of the involved ICDs by spring 1998.

6. *Refocus and restructure the drug discovery research effort*

NCI has established an *ad hoc* panel to assess its existing program for the development of therapeutics. One of the important responsibilities of this panel will be to develop recommendations for the future role and direction of the National Cancer Institute's (NCI) Developmental Therapeutics Program (DTP). However, DTP already has terminated (as of January 1997) its drug-screening program of natural products extracts against HIV. A DTP Working Group of nongovernmental advisors will review the NCI cell-based screening program of pure synthetic and natural product compounds and determine its future direction.

7. *Augment basic research on AIDS-related opportunistic infections and facilitate transfer of new findings to early clinical evaluation*

NIH has placed a high priority on research on AIDS-related OIs. Several ICD initiatives are planned in FY 1997 and 1998 to target research on OI pathogens. In addition, specific strategies have been included in the FY 1998 NIH Plan for HIV-Related Research that will facilitate research to better understand OI pathogens and their mechanisms of pathogenesis as well as accelerate the discovery, development, and evaluation of potential drug regimens for the treatment and prevention of AIDS-related OIs. NIH will continue to encourage translational research and collaborations between laboratory and clinical investigators and industry.

8. *Strengthen the scientific base for the assessment of complementary and alternative medicine therapies for HIV disease*

The NIH Office of Alternative Medicine (OAM) will assist OAR in establishing an advisory panel on CAM research for HIV disease that will identify and distinguish therapies with apparent promise from those with potential harm. To improve the quality of this area of research, OAM will convene several research methodology workshops to educate individuals interested in pursuing complementary and alternative medical approaches to the treatment of HIV/AIDS.

9. *Reorganize procedures to ensure that Regional Primate Research Centers are available and responsive to non-Center-affiliated scientists*

An outside panel of experts is reviewing the National Center for Research Resources (NCRR)-sponsored Regional Primate Research Centers (RPRCs) and will develop plans for operating these facilities with maximum economy and efficiency. In FY 1997, OAR provided NCRR with an additional $2.5 million to support a special initiative to increase use of RPRC animals and facilities by non-Center investigators. The applications submitted in response to this initiative are currently under review by DRG study sections.

10. *Strengthen AIDS Research Centers to promote multidisciplinary research on the disease*

NIAID has implemented a series of program modifications to increase the number and focus of required cores and initiate a “rolling” competition in which several new and/or re-competing Centers for AIDS Research (CFARs) will be renewed each year beginning in FY 1998. Several ICDs, including NCI, National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), National Heart, Lung, and Blood Institute (NHLBI), and National Institute of Child Health and Human Development (NICHD), may cosponsor the CFAR program with NIAID.

NIMH is implementing several new strategies to ensure that its AIDS Research Centers continue to be of high scientific merit, are consistent with the needs of a maturing field, and are cost-effective. NIMH is disaggregating some of the outstanding research projects and converting these to R01s in order to stimulate innovative research and contain costs.

11. *Ensure that central repositories of biomedical specimens and databases are of the highest quality and accessible to qualified investigators*

NIH has and will continue to ensure that repositories and databases are scientifically designed and that data and specimens are made available to test specific scientific hypotheses. To ensure that repositories and databases are more widely accessible to all qualified investigators, NIAID and NHLBI have established review mechanisms for collaborators seeking access to the data and biological specimens collected from NIH-funded behavioral, epidemiology, and clinical HIV studies. The NIAID "Specimen Repository Guidelines" and NHLBI guidelines are now widely available within the research community.

12. *Upgrade the NIH AIDS Research Information System and increase the information base*

OAR and the Division of Computer Research and Technology have developed a prototype user-friendly, Web-based interface to OAR's AIDS Research Information System (ARIS) database. This prototype permits data searches of Computer Retrievel Information Systems Program (CRISP) project descriptions and ARIS budget information. In addition, OAR is working with the Office of Extramural Research to develop and test a prototype system that would collect descriptions of ongoing research as well as journal citations that could be linked to the ARIS database. Other potential linkages to ARIS being explored include those to either modified annual progress reports, updated grant application abstracts, or Information for Management Planning, Analysis, and Coordination (IMPAC-2) databases.

13. *Develop and implement a clear definition of AIDS and AIDS-related research through an evolving process*

Beginning in FY 1999, NIH will use the annual Plan for HIV-Related Research as the formal definition of what constitutes AIDS research. The ICDs will use this definition in coding and reporting their AIDS-related programs and projects. The implementation of IMPAC-2 will permit NIH to better track and monitor AIDS-related programs and permit the ICDs to better code their AIDS-related efforts.

14. *Preserve a strong OAR to provide leadership and coordination to the entire NIH AIDS research program*

In response to the charge given by the Task Force, OAR has worked with the ICDs to develop the following plan and incorporate Task Force recommendations into the FY 1999 NIH Plan for HIV-Related Research. As described in more detail below, OAR will continue to facilitate the coordination of the NIH AIDS research program in accordance with the annual NIH Plan and track the ICDs' efforts in implementing the Plan.

<u>The Roles of OAR and ICDs in Implementing Task Force Recommendations</u>

OAR will continue to facilitate cross-ICD communication and collaboration and build consensus among the ICDs to ensure that the NIH AIDS research program is developed in accordance with the NIH Revitalization Act of 1993. OAR will continue to be guided by the Task Force recommendations as it sponsors state-of-the-science workshops and conferences, reviews requests for OAR Discretionary Funds, sponsors the NIH HIV/AIDS Seminar Series, and participates in NIH and other

national and international meetings to review, evaluate, and plan AIDS research. Most important, OAR will continue to utilize the recommendations as it develops the annual NIH Plan for HIV-Related Research, which serves as the basis for the annual NIH AIDS research budget.

The ICDs, however, are responsible for the actual implementation and management of the programs and projects that make up the NIH AIDS research portfolio. The ICDs, in close coordination with their Advisory Councils and nongovernmental advisors and experts, will continue to review existing programs and, when appropriate, identify scientific areas that require new PAs or initiatives so that ICD-sponsored AIDS research efforts are focused or refocused on the most promising research opportunities or needs and that AIDS research resources are most efficiently and effectively used.

OAR and the ICDs will continue to collaboratively develop the annual NIH Plan and monitor the scientific progress to ensure that the NIH AIDS programs continue to evolve as the pandemic changes. The continual monitoring and managing of the NIH-funded AIDS programs will be crucial to ensure that the spirit and intent of the Task Force recommendations are, when appropriate, pursued and implemented. This collaboration is essential to guarantee that the programs supported by the ICDs fit into a comprehensive and organized AIDS program so that duplication between programs is eliminated and funds, specimens, databases, and studies are used efficiently and effectively to answer the key scientific questions that remain about HIV infection and its sequelae.

NIH AIDS Research Program Evaluation Working Group Recommendations

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I. INVESTIGATOR-INITIATED RESEARCH

Increase support for and improve peer review of investigator-initiated research

Recommendation 1 [Working Group Report, p. 6, No. 1]

The proportion of the NIH AIDS research budget allocated to support unsolicited investigator-initiated research should be approximately doubled.

Current Status

A review of the total AIDS research portfolio in 1994 revealed that the proportion of the AIDS research budget allocated to funding unsolicited investigator-initiated research grants was approximately 24 percent of the total AIDS research budget. However, for other areas of research across the NIH, the total proportion of the budget allocated for such grants is nearly double that proportion. While there were valid reasons in the past for this disparity in the funding mechanisms, since 1994 the OAR has placed a high priority on increasing the available pool of resources for R01 grants. In budget discussions each year with the ICDs, the OAR has encouraged the ICDs to increase the R01 allocation and discouraged whenever possible the use of mechanisms that would target research through RFAs. As a result of these efforts, it is estimated that funding for investigator-initiated research in FY 1998 will represent a 52-percent increase over FY 1994.

Future Actions

NIH concurs with the goal of this recommendation and will continue to work with the ICDs through each budget cycle to increase the pool of available funds for such grants and continue the trend already established.

Recommendation 2 [Working Group Report, p. 6, No. 2]

Selected members of AIDS-related IRGs should participate in the OAR's process for setting research priorities. As an integral part of the IRG process, these individuals, in concert with DRG and OAR staff, should familiarize their IRG members with the OAR- and ICD-defined AIDS research priorities.

Recommendation 3 [Working Group Report, p. 6, No. 3]

Scientific Review Administrators of AIDS-related IRGs should be included as members of the OAR Coordinating Committees corresponding to their area of expertise.

Recommendation 4 [Working Group Report, p. 6, No 4]

The OAR, in concert with the ICDs, should inform the ICD advisory bodies and councils of the NIH AIDS research priorities as outlined in the NIH Plan for HIV-Related Research.

Recommendation 5 [Working Group Report, p. 6, No. 5]

The OAR should develop a strategy to distribute the NIH Plan for HIV-Related Research to the scientific community and other interested parties.

Current Status

The NIH Act of 1993 (Public Law 103-43) provides that the Director of the OAR shall "establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of NIH; ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; ensure that the Plan establishes objectives regarding such activities; and ensure that the Plan serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of specific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan."

The law further provides that "the Director of the Office shall ensure that the Plan provides for basic research; provides for applied research; provides for research that is conducted by the agencies; provides for research that is supported by the agencies; provides for proposals developed pursuant to solicitations by the agencies and for proposals developed independently of such solicitations; and provides for behavioral research and social sciences research."

Within NIH, the OAR established six Coordinating Committees to develop plans for specific areas of AIDS/HIV research: Natural History and Epidemiology, Etiology and Pathogenesis, Therapeutics, Vaccines, Behavioral Research, and Information Dissemination. Each of these committees also were charged to address training needs in these areas. The members of the Coordinating Committees are selected by the OAR from the staff of those NIH ICDs with the most significant research portfolios in the scientific areas. The Coordinating Committees develop the first draft of the annual NIH Plan for HIV-Related Research through a series of meetings, utilizing the previous year's plan as the framework for their deliberations. The charge to the members of the Coordinating Committees is to update the Plan, viewing the process from the perspective of the overall priorities of the scientific areas, not from an ICD-specific perspective.

The draft Plan developed by the Coordinating Committees is then provided to each ICD Director and ICD AIDS Coordinator, who provide ICD-specific recommendations and suggestions for additions or other changes. The Coordinating Committees meet to consider all of the ICD recommendations and to make changes in the draft Plan. They also consider areas of overlap within the Plan to determine the appropriate way to address them.

To obtain broad participation by non-NIH experts in this process, OAR convenes a workshop to review and revise the draft Plan. The attendees at this workshop include ICD Directors and AIDS Coordinators; Coordinating Committee members; invited experts from universities, research institutes, and industry; as well as representatives of community organizations. Meeting in working groups for each of the six areas of emphasis, these NIH scientists, non-Government researchers, and community representatives work together to form a consensus regarding the

formulation and prioritization of the objectives that will guide research within each area of emphasis. Through this process, involving hundreds of scientists, clinicians, program managers, community representatives, and other experts from a wide range of fields, a consensus is reached regarding the goals and directions required to move AIDS research forward.

Future Actions

NIH continues to support the principle of separation of scientific review from program prioritization, which has traditionally been the role of ICD program staff and advisory councils. However, the NIH recognizes that scientific review does not occur in a vacuum. Scientific review groups, ICD staff and advisors, and the OAR would benefit from stronger interaction based on common scientific goals. Toward that end, DRG, OAR, and the ICDs have begun to work together to develop mechanisms to improve communication and encourage mutual awareness.

NIH concurs that SRAs should be included as members of the OAR Coordinating Committees, and OAR will request such nominations from DRG. The chair of each AIDS-related study section also will be invited to attend the public workshop that involves both NIH and non-Government experts in crafting the annual Plan. While it will be important for the study section members to be mindful of the independence and separation of programmatic priorities and scientific merit, NIH believes it would be appropriate for the chairs of the study sections to inform the other members of their study sections about the scientific priorities and strategies set forth in the Plan.

NIH also concurs that the ICD advisory bodies and councils should be fully apprised of the NIH AIDS research priorities as outlined in the Plan, and OAR will work with the ICDs to determine the most appropriate mechanism to brief members of these bodies and/or to distribute copies of the Plan to all members of the councils and appropriate advisory groups.

NIH concurs that the NIH AIDS research plan should be more widely distributed and has initiated a number of strategies to accomplish this. The FY 1998 Plan has been posted on the OAR home page of the NIH World Wide Web site, increasing its immediate availability. The FY 1998 Plan was made available on diskette and through an order form at the XI International Conference on AIDS. OAR scientific staff will continue to make presentations on the Plan and to distribute copies of it to scientists and community groups at professional meetings and workshops.

Recommendation 6 [Working Group Report, p. 6, No. 6]

> *AIDS-related grant proposals should include a discussion of how the proposed investigation relates to the research priorities detailed in the NIH Plan for HIV-Related Research.*

Current Status

The scientific, technical, and medical significance of proposed grants has been evaluated by NIH study sections, while ICD program staff and advisory councils have evaluated proposed research

in terms of program priorities, relevance, and interests. NIH continues to support the principle of separation of scientific review from program prioritization. NIH recognizes, however, that scientific review does not occur in a vacuum. The non-Government experts who serve on NIH study sections are well able to monitor the opportunities and directions for progress and development in a scientific field as presented in new grant applications since the reviewers also are researchers and applicants in these fields; however, it is ICD staff and advisors who evaluate program needs and define goals. Clearly, both groups would benefit from being informed by the other.

Regarding the AIDS relevance of applications, it is important to note that ICD referral guidelines address this issue, and it is assessed at the time of referral/assignment by the DRG Referral Office staff. In addition, the Public Health Service (PHS) 398 application kit defines AIDS relevance, and the applicant is expected to address this issue if ambiguity exists.

Future Actions

DRG plans to work with the OAR and ICDs to develop mechanisms to improve communication and encourage mutual awareness. One such mechanism could be the inclusion of AIDS study section members (e.g., study section chairs) as well as the SRAs of AIDS study sections in OAR planning groups. While it will be important for these study section members to be mindful of the independence and separation of their programmatic and review responsibilities, there would appear to be nothing inappropriate in their briefing the entire study section on OAR planning activities at the outset of study section meetings or at a special session the evening before the meeting.

DRG also will work with the OAR and ICDs to explore the possibility of providing supplemental guidance to applicants that would include a request that they address the issue of how their proposed study relates to the NIH Plan for HIV-Related Research. Study section members should additionally be instructed to express any concerns about the AIDS relevance of an application in an administrative note to ICD staff.

Recommendation 7 [Working Group Report, p. 7, No. 7]

> *It is critical that the DRG work with OAR and the ICDs to provide IRGs with high-calibre, mature, and diverse scientists and clinicians. DRG should investigate possible mechanisms to ensure high-quality reviews responsive to the changing scientific issues. Such mechanisms might include working with learned societies to identify distinguished scientists with a broad range of expertise to serve on IRGs, making greater use of voting* ad hoc *members, and exercising flexibility on the term limits for IRG participation.*

Current Status

DRG strongly endorses this recommendation to strengthen the IRGs and is already developing plans to work more closely with ICD staff and scientific societies to identify and use high-quality

reviewers as members of study sections reviewing AIDS-related research grant applications, including Small Business Innovative Research (SBIR) program grant applications.

Future Actions

DRG will continue to work with ICD staff and professional scientific societies to develop plans to further efforts to identify and use high-quality reviewers in its AIDS study sections and implement these plans as appropriate.

Recommendation 8 [Working Group Report, p. 7, No. 8]

> *DRG should be responsive to the evolving character of AIDS research and modify IRG composition or define new IRGs as needed. The Working Group believes that the existing AIDS-related IRGs should be redefined and reconfigured to reflect the current scientific priorities for AIDS research, particularly as they relate to vaccine and prevention science research needs.*

Current Status

This core recommendation is timely because of the pending alignment of AIDS-related study sections of NIMH, NIDA, and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) with DRG. As part of this change, the DRG is planning to assess the overall organization of the AIDS-related study sections and will incorporate the concerns expressed in these recommendations in this process.

Future Actions

Plans to assess the organization of the AIDS-related study sections that address the concerns expressed by the Task Force will be implemented. With regard to the specific areas of prevention science and vaccine research, consideration will be given to a better focus of review, which may be accomplished in part by reviewing these areas in Special Emphasis Panels (SEPs). Perhaps these areas also can be examined in a more broad, trans-NIH fashion, e.g., by creating a focus of review for vaccine-related research of various types.

Recommendation 9 [Working Group Report, p. 8, No. 9]

> *Given the crucial importance of training for the research enterprise, the OAR should establish a Coordinating Committee on Training and Infrastructure, with the same responsibilities as other OAR Coordinating Committees.*

Recommendation 10 [Working Group Report, p. 8, No. 10]

> *OAR Coordinating Committee on Training and Infrastructure should review the NIH Plan for HIV-related research and address a wider range of NIH training mechanisms*

(such as the K awards, supplements, and predoctoral research opportunities). The Plan should include strategies for the systematic outcome evaluation of training awards.

Current Status

Training and infrastructure issues are integral to all of the scientific areas of the NIH Plan for HIV-Related Research. Currently, NIH supports intramural and extramural research resource programs, including grants for training researchers in diverse HIV-related scientific areas, programs for maintaining animal facilities for animal model research, and programs for constructing or improving existing facilities and equipment.

Domestic and international training and infrastructure have been and will continue to be distinct areas of consideration in the NIH AIDS planning and budgetary processes. The FY 1998 Plan for HIV-Related Research contains a special section on AIDS training and infrastructure that was developed by the senior OAR Health Science Administrators in collaboration with their respective Coordinating Committees.

Future Actions

To address these crosscutting areas, OAR will continue to utilize the diverse perspectives and experience of the members of the existing OAR Coordinating Committees through a formally convened OAR planning committee for HIV-related training and infrastructure. The OAR will enlist the chairs of each of the currently existing Coordinating Committees to serve on this planning committee. In considering plans for domestic and international training and infrastructure issues, the committee will solicit input from the Coordinating Committees and consider issues and recommendations from the ICDs and non-Government sources. Further, this planning committee will review and develop recommendations on domestic and international training and infrastructure funding proposals submitted to the OAR Discretionary Fund. Once this committee is convened, a review and consideration of training mechanisms and outcome evaluation of training awards will be undertaken.

Recommendation 11 [Working Group Report, p. 8, No. 11]

Innovative mechanisms to provide short-term (2–3 year) support of young investigators at levels sufficient to initiate quality research programs should be developed.

Current Status

NIH and its component ICDs are very supportive of developing innovative mechanisms and more effectively utilizing existing mechanisms to provide short-term funding to allow more new investigators to achieve their potential in biomedical, behavioral, and social science research and establish quality research programs. NIH currently provides support for new investigators through a variety of award mechanisms for research project grants. New investigators often are

not aware of some of these mechanisms, and a few of the mechanisms could be modified to make them more attractive. Some grant mechanisms are employed by all ICDs, while others are used to address specific ICD or programmatic needs. The most common mechanisms used include but are not limited to R03, R29, K01, K08, K11, and F32 awards; developmental funds in connection with the CFARs; and competitive supplements to General Clinical Research Centers (GCRCs) or other grants.

Standard Research Project Grant Awards

R29 First Independent Research Support and Transition (FIRST) Award: The R29 awards for new investigators have a cap of $350,000 direct costs over a 5-year period, an average of $70,000 per year. These grants are extensively used by most ICDs and are highly appropriate for many areas of research. Some new investigators do not apply for grants through this mechanism because their institutions require them to obtain a larger proportion of the salary than can be supported through an R29. In addition, research involving nonhuman primate or other animal models in AIDS research as well as research in the areas of clinical and health sciences often cannot be funded with such limited budgets.

However, new investigators have the advantage that specific guidelines for the evaluation are included as part of the review of R29 grant applications. For example, the level of preliminary data required or expected in an R29 application is less than in an R01, and this should be reflected in the final score. Additionally, some ICDs such as NCI and NIAID have encouraged new investigators by awarding R29 grants with higher numerical or percentile scores than R01s.

Currently, National Institute of General Medical Sciences (NIGMS) encourages new investigators by selectively paying highly meritorious R01 (as well as R29) applications from new investigators or "reaching" for their R01 grants, even if beyond the nominal pay line. These include new investigators conducting AIDS-related research. Several other ICDs have "selective pay" approval authority that primarily permits them to fund research that addresses critical scientific gaps.

Grants Designed for Development of New Research Areas

R55 James A. Shannon Director's Awards: These awards were initiated several years ago in response to the problems that faced many investigators new to a field when many IRGs required extensive preliminary data to be presented in grant applications. This requirement made it difficult for applicants with highly promising proposals but very limited data. These awards also were used to support investigators on R01 grants who needed a "bridge in funding" to more fully develop a recently initiated project. Shannon awards are limited to $80,000 in direct costs plus only $20,000 in indirect costs for 2 years. Initially, funds for the first year were provided from the NIH Director's budget. Nearly all ICDs have utilized this funding mechanism.

R21 Exploratory/Developmental Grants: Some ICDs use this funding mechanism to provide support for projects to acquire preliminary data. While useful for start-up funds, these grants often are too limited in time or scope to develop a sustainable program for a new investigator. When successful, these grants can quickly move young investigators into independent R01s. Both

NIGMS and NCRR are issuing initiatives for exploratory grants (R21) for innovative high-risk research projects for which preliminary results may be lacking.

R03 Small Grants: These awards have been used to support AIDS-related research and are usually ICD or program specific, generally in response to an RFA or PA. Each ICD sets the dollar limits for various R03 programs, with awards generally for 2 or 3 years. The dollar limit imposed on the individual awards (< $50,000 direct costs) is usually insufficient to accommodate biomedical research on nonhuman primates or on human subjects.

NIMH and NIDA are using the R03 mechanism to support the relatively new Behavioral Science Track Award for Rapid Transition (B/START), which is specifically intended for the initiation of independent research careers. Newly independent behavioral science investigators are invited to submit applications for small-scale, exploratory, or pilot studies for 1 year (NIMH) or 2 years (NIDA). Of 91 B/STARTs funded by NIMH in FY 1994 and FY 1995, 13 were in the area of HIV/AIDS research.

Awards for Transition From Training to Independent Careers

Some ICDs, such as NIAID, NCI, NIMH, and NCRR, have developmental funds available through Center Grants (M01, P30, P50, or P51) that can be used for pilot projects. These funds are administered through the individual centers and are limited to the centers involved.

NCRR also supports several programs to promote the development of new research investigators:

- Through competitive supplements to GCRC grants (M01), three programs (the Clinical Associate Physician Program, the Minority Clinical Associate Physician Program, and the Clinical Research Scholar Program) are available to further the training of physicians and dentists toward becoming independent clinical investigators, under the guidance of mentors who are established clinical research scientists.

- NCRR also supports the development of multidisciplinary veterinary researchers to become independent investigators through a 5-year Special Emphasis Research Career Award. These programs are not specific for AIDS research but include new investigators training in AIDS-related research.

A number of ICDs support new clinical investigators through training mechanisms that have a transition component, including the K08 (Clinical Investigator Award) and K11 (Physician Scientist Award). These grants are designed to provide the opportunity for promising medical scientists to develop into independent research investigators. The awards provide salary support for 4 to 5 years. K08 awardees are usually encouraged to apply for independent R01 research support during the award period.

Future Actions

NIH has and will continue to utilize a variety of funding mechanisms to meet various ICD and programmatic needs to support new investigators in the field of AIDS research. ICD and OAR

staff will support options to make existing awards more attractive to beginning investigators in AIDS-related research and publicize alternative mechanisms through which new projects may be funded. To facilitate rapid implementation, the OAR will set a priority on using a portion of its FY 1997 OAR Discretionary Funds to support highly meritorious applications for R01s and other funding mechanisms from new investigators with innovative ideas for AIDS-related research.

Recommendation 12 [Working Group Report, p. 9, No. 12]

Many investigator-initiated research grants in areas unrelated to HIV/AIDS objectives, held by distinguished senior scientists, generate findings that may be relevant to questions in AIDS research. To encourage these laboratories to explore AIDS-related avenues of research, a program should be established that offers supplemental funding to support postdoctoral fellows or graduate students to carry out AIDS-related research.

Current Status

NIH concurs with the Task Force recommendation that ICD programs must continue to provide supplemental funds to support predoctoral and postdoctoral students to ensure future generations of highly qualified researchers in AIDS-related research. The ICDs utilize a variety of programs and funding mechanisms to attract new investigators into AIDS research.

Several examples of such programs include the R03 small grant programs, which often support pilot AIDS research studies that result in sufficient data to serve as the basis of R01 applications; the R21 exploratory/developmental grant program, which supports investigations by researchers in other fields to conduct AIDS-related studies; and R55 Shannon awards, which support new investigators with highly promising proposals but limited supportive data.

NIH also utilizes competitive supplements to existing investigator-initiated research grants and center awards, such as NCI Cancer Centers awards, to stimulate cross-disciplinary research and initiate AIDS-oncology training programs. In addition, OAR provided FY 1996 Discretionary Funds as supplements through the ICDs to support new investigators in AIDS research. NIMH supports the Dissertation Research Grant and the B/START program.

Future Actions

NIH will further strengthen ongoing and new programs and identify, when needed, new funding mechanisms to provide future opportunities to support new investigators in AIDS-related basic and clinical biomedical and behavioral research.

Recommendation 13 [Working Group Report, p. 9, No. 13]

NIH should develop programs for AIDS-related research training explicitly tailored and targeted to ethnic minority individuals, primarily at the postdoctoral level. Rather than

simply supplementing existing grants, these programs should involve collaborative mentoring activities in research projects defined by the minority scientists. Programs should include intense and long-term mentoring and support in the NIH grant application process. A criterion of evaluation of these programs should be the number of new NIH-funded principal investigators (PIs) of ethnic minority background.

Current Status

The FY 1998 NIH Plan for HIV-Related Research identifies the need to develop and expand programs for AIDS-related research training tailored and targeted to minority researchers, primarily at the postdoctoral level. A number of prestigious committees and commissions previously have recognized the need to increase the number of ethnic minority individuals entering biomedical and behavioral research and health fields in general (e.g., the 1989 Task Force on Women, Minorities, and the Handicapped in Science and Technology; the report of the National Research Council on *Meeting the Nation's Needs for Biomedical and Behavioral Scientists*; and the 1985 report of the Institute of Medicine [IOM] on *Personnel Needs and Training for Biomedical and Behavioral Research*). NIH has identified the training of minority researchers generally as a high priority, by establishing the NIH Office of Research on Minority Health (ORMH) with significant budgetary support. A number of NIH training programs have been developed to help further this priority; some of these programs place a special emphasis on HIV/AIDS. They generally fall within the categories of mentoring, supplements, fellowships, and collaborations.

Examples of mentoring programs include (1) the minority health initiative established within the Fogarty International Center (FIC) AIDS International Training and Research Program (AITRP), which was initiated with ORMH support but is now funded by FIC; (2) NIDA's mentoring initiative involving 10 Historically Black Colleges and Universities, which involves a series of small conferences, training workshops, and technical assistance activities aimed at increasing the numbers of minority scientists involved in drug abuse research, including HIV/AIDS-related studies; and (3) NIAID's Enhancement Awards for Underrepresented Minority Researchers in HIV/AIDS.

A number of ICDs support supplements for minority students, fellows, and new investigators associated with investigator-initiated research projects, for example the Research Supplements for Underrepresented Minority Individuals in Postdoctoral Training program. Since 1989, 34 percent of NIAID grantees who participated in this program have succeeded in obtaining an independent NIH grant.

NIH also supports pre- and postdoctoral fellowships for minority scholars in HIV/AIDS research. For example, NIMH supports a minority fellowship program that allocates funds to professional organizations for predoctoral training of minority students in AIDS research at institutions throughout the country. In addition, the NIMH Office on AIDS participates in the NIMH Career Opportunities in Research Education and Training Program. This program is directed specifically to 4-year colleges and universities that serve a substantial number of students of one or more

racial/ethnic minority groups who are underrepresented in biomedical and behavioral sciences relevant to research in the mental health fields. NIMH also uses the K01 Research Scientist Development Awards to support research for new minority scientists to help establish their research programs.

NIH encourages and supports collaborations between its ICDs and between ICDs and universities and other external organizations to promote minority researchers in HIV/AIDS research. For example, a pilot program in FY 1996 has produced 12 collaborative research pairs of investigators from NCRR-sponsored Research Centers at Minority Institutions (RCMI), NIAID's CFARs, and NIMH's AIDS Research Centers.

Future Actions

NIH fully agrees with the long-term goal of this recommendation of further increasing the number of ethnic minority PIs. NIH has a historical commitment to enhancing opportunities for minority AIDS investigators, as illustrated by the number of active programs throughout the ICDs providing both funding and mentoring opportunities noted above. Since many of these programs already exist (some were initiated while the Task Force evaluation was in process), NIH will more aggressively disseminate information about the existing programs with the immediate objective of substantially increasing the number of participants. NIH will continue to develop more creative, efficient, and effective ways to attract potential participants in these programs and to find ways to include minority HIV/AIDS researchers in other training, mentoring, and career development programs that already exist but have not yet been specifically employed for AIDS research.

NIH will closely evaluate the effectiveness of these programs in increasing the number of participating ethnic minority individuals. However, evaluation of the success of these programs by the number of new NIH-funded PIs of ethnic minority background is difficult, because monitoring of incoming grant applications depends on the applicant voluntarily self-identifying as a member of an ethnic minority group, and not all applicants choose to do so. Thus, followup may be incomplete.

Recommendation 14 [Working Group Report, p. 9, No. 14]

> *OAR should investigate the possibility of extending the AIDS Loan Repayment Program (LRP) to forgive student loan debts for postdoctoral fellows working in AIDS research outside of the NIH intramural program.*

Current Status

The law authorizing the AIDS LRP states that it will be a program for qualified health professionals who "agree to conduct, as employees of the National Institutes of Health, research with respect to acquired immune deficiency syndrome." Thus, the current law does not allow non-NIH scientists to participate in the LRP.

Future Actions

A change in the Federal law authorizing the AIDS LRP would require the support of NIH and the Department of Health and Human Services (DHHS) and would require significant programmatic justification and economic analysis. Several other loan forgiveness programs modeled on the AIDS LRP have been authorized by law. Such a change for one program would also have ramifications for other similar programs. OAR will raise the issue of expanding this program with the AIDS Loan Repayment Advisory Committee and encourage it to investigate the feasibility and desirability of changing the law governing the program.

II. AIDS VACCINE RESEARCH

Establish a restructured trans-NIH vaccine research effort

Recommendation 15 [Working Group Report, p. 10, No. 1]

The entire AIDS vaccine research effort of the NIH should be restructured. A trans-NIH vaccine program should be established with leadership and oversight provided by distinguished, non-Government scientists.

Current Status

The NIH agrees with the Working Group that the development of a safe and effective vaccine must be one of the highest priorities in the AIDS research effort. The goals and focus of the ongoing vaccine efforts within NIH are consistent with those expressed in the Working Group Report, specifically coordination across ICDs and between intra- and extramural investigators, integration of basic research advances in immunology and pathogenesis, and heightened visibility of the vaccine research and development efforts.

NIH also agrees that the overall vaccine effort should be coordinated and centralized at NIAID and should operate in conjunction with a proposed AVRC chaired by a distinguished non-Government scientist. Dr. David Baltimore, a Nobel Laureate with expertise in retrovirology and immunology, was named by the NIH on December 12, 1996, to chair the AVRC. He will officially serve as a consultant to the NIAID working with program staff scientists in its Division of AIDS (DAIDS) but will work with the AVRC and other ICDs to coordinate HIV/AIDS vaccine research across the NIH.

Language in the report also recommends the establishment of a separate division within NIAID to coordinate the work of the AVRC. While the NIH sees a value in the visibility, advice, and perspective that such a committee could bring to the development of an HIV vaccine, it does not see the necessity of establishing an independent NIH center or a division within NIAID to support these activities.

A committee of scientists with expertise in all areas of vaccine development will further help highlight important areas of research, provide invaluable advice and guidance in identifying high-priority areas of research and development, and help find ways to quickly and flexibly marshal the resources to achieve the prioritized research or development. The composition of such a committee is critical to achieve the overall objective. The committee will (1) be small, with a balance of research and development perspectives; (2) provide an external perspective in helping to define and implement priorities; and (3) support rapid and efficient resource mobilization for specific “targeted” research tasks.

The NIH Director, OAR Director, and Directors of NIAID and NCI and Dr. Baltimore have considered potential members for the AVRC to provide a balanced perspective for advice on vaccine research and development. Members of the AVRC met on February 17, 1997, in Bethesda, Maryland.

Future Actions

The AVRC, working with the NIH HIV/AIDS Vaccine Coordinating Committee, will develop the vaccine component of the annual NIH Plan for HIV-Related Research. A series of regional meetings will be convened by the AVRC over the next 2 years to solicit scientific input into HIV/AIDS vaccine design, research, and development.

Recommendation 16 [Working Group Report, p. 11, No. 2]

> *A National AIDS Vaccine Task Force (NAVTF), chaired by the Director of OAR, should be established in the White House Office of the National AIDS Policy, with responsibility for coordinating all Government-sponsored vaccine programs.*

Current Status

In response to a request from the President in 1996, the OAR coordinated the development of the Federal Biomedical and Behavioral Research Plan and Budget for HIV and AIDS that was provided to the White House Office of National AIDS Policy. A coordinated AIDS/HIV vaccine plan for FY 1997 has been developed by representatives of agencies of the U.S. Government that have planned or ongoing activities in this area, i.e., the NIH, the Department of Defense (DoD), the Food and Drug Administration (FDA), the Department of Veterans Affairs (VA), and the Centers for Disease Control and Prevention (CDC). Apart from this plan, strong research collaborations exist between the Government agencies. NIH is evaluating the appropriateness of domestic and international sites for Phase II and Phase III vaccine trials with the support from CDC, DoD, and VA. NIH and DoD work closely with the FDA to evaluate the safety and efficacy of vaccine candidates.

Future Actions

At this time, OAR believes that it would be more productive to have scientific staff at the different Federal agencies involved in HIV/AIDS vaccine research meet regularly throughout the year on topics of emerging interest, rather than just for budget and planning efforts. To encourage coordination between agencies of the Federal Government, OAR will incorporate representatives of other agencies in planning meetings, starting in the spring of 1997. OAR will work closely with NIAID to sponsor and support the PHS AIDS Vaccine Research and Development subgroup to continue cross-agency and cross-institute scientific updates and discussion of advances and obstacles in both extramural and intramural HIV/AIDS vaccine research. In addition, OAR will continue to encourage the strong informal links that have formed between staff in the NIH, CDC, DoD, FDA, and VA. It is expected that the recently formed AVRC will provide further input and advice on this recommendation.

Recommendation 17 [Working Group Report, p. 12, No. 3]

NIAID, in partnership with other ICDs with complementary expertise, should promptly develop a comprehensive plan for HIVNET's organization, Governance, research, and funding. This plan should be reviewed in 1996 by a joint OAR/ICD-convened panel of extramural experts in behavioral, social, epidemiological, prevention, pathogenesis, and treatment research as well as vaccine research. If reviewers determine that there are significant deficiencies in the plan, funds could be released for retargeting to other essential areas of AIDS research.

Current Status

The recommended plan was developed in 1996 by HIVNET investigators and NIH staff. In June 1996, NIAID and OAR convened a multidisciplinary panel of experts to conduct a review of the HIVNET organization, governance, research, and funding. This review included participation of representatives from other ICDs with research expertise relevant to HIVNET's activities. This review was conducted under the auspices of the NIAID AIDS Research Advisory Committee (ARAC). A report of the review and the recommendations was presented to the ARAC and accepted by that group in September 1996. A summary of the review and recommendations also was presented to OARAC in October 1996.

The panel expressed confidence in HIVNET. They found the scientific plan and program of research to be sound. In addition, the panel noted that there had been considerable progress and maturation of the HIVNET since the time of the NIH AIDS Research Program Evaluation Task Force Report. The ARAC panel provided a number of constructive recommendations to further improve the HIVNET, including the following:

- HIVNET should be continued and should give priority to its original mission, which is to provide the capacity for prompt and scientifically sound assessment of vaccine efficacy both domestically and internationally.

- HIVNET must continue to maintain a strong multidisciplinary approach to maintain or develop its capacity for evaluating both vaccine and nonvaccine interventions.

- In addition to the ongoing program of research related directly to vaccine efficacy trials, HIVNET's domestic and international cohorts provide a valuable resource for evaluating other biomedical and behavioral interventions for preventing sexual, parenteral, and perinatal transmission of HIV. Inter-institute/agency collaboration for microbicidal and perinatal transmission studies and OAR-based coordination for behavioral studies are essential for defining the scope of, and setting priorities for, these non-vaccine-based activities.

- The management and oversight of HIVNET need to be more clearly defined, specifically with regard to (1) the roles and responsibilities of HIVNET contractors and DAIDS/NIAID staff; (2) the process that ensures the highest scientific peer review of

HIVNET-sponsored trials; and (3) the availability of specimens to other laboratories conducting related research on vaccine development and on the immunology and virology of HIV infection.

- For non-vaccine-based activities, prioritization and implementation plans should include clearly articulated guidelines for the choice of product or interventions. For microbicides and perinatal transmission research, these guidelines should consider the potential global availability of products, the establishment of biological endpoints, and the development of individual rather than community intervention strategies. Behavioral research should focus on descriptive or methodological studies essential for the conduct of vaccine trials. When promising behavioral interventions have been identified as suitable for testing in the HIVNET, they should be tested using HIV infection as the trial outcome measure.

Future Actions

NIAID will continue to fund the HIVNET as a master contract. Program staff will continue to work with the HIVNET investigators to implement the research priorities outlined in the scientific agenda proposed by the group and endorsed by the external review panel. HIVNET investigators and staff are developing a plan to implement the Task Force recommendations and to incorporate them into the operation of the HIVNET. For example, improvements in the peer-review process for studies and sites recommended by the Task Force are being implemented. Where needed, NIAID program staff will continue to seek assistance from the OAR in fostering inter-ICD collaboration.

III. RESEARCH ON THE HUMAN IMMUNE SYSTEM

Augment research efforts to better understand the human immune system

Recommendation 18 [Working Group Report, p. 13, No. 1]

OAR should convene a series of workshops of expert immunologists to develop a plan to accelerate progress in understanding the following:

- *The basic biology and development of human immunocompetent cells and of the unique aspects of the physiology of the human immune system.*
- *How HIV or SIV perturbs the human or primate immune system to impair the function of and destroy immunocompetent cells.*
- *Why normal replacement mechanisms are unable to restore a functional immune system in infected individuals.*
- *Why normal host defenses are unable to ultimately contain HIV infection.*

Current Status

The pace of discoveries in basic immunology in the past 20 years has been phenomenal. OAR strongly agrees on the importance of building upon these advances and making further progress in understanding basic aspects of the human immune system. For instance, while the mouse model system has been instrumental in deciphering many basic aspects of the immune system, its usefulness has been limited. Not all of the findings from this model can be directly translated to the human system because of its intrinsic heterogeneity and complexity. As a result, studies of HIV/SIV (simian immunodeficiency virus) immunology in human and primate models are underrepresented in the NIH scientific portfolio.

Future Actions

OAR will, in collaboration with relevant ICDs, convene a series of workshops to address the specific scientific needs highlighted by this recommendation. These workshops will be chaired by outstanding AIDS and non-AIDS immunologists and will be instrumental in the development of the overall scientific agenda in AIDS. The first workshop will be convened in late 1997 to address issues related to T-cell repopulation observed after therapeutic interventions that have significant effects on CD4+ T-cell numbers. It is anticipated that these meetings will provide the intellectual and scientific framework necessary to foster productive interactions among scientists. By sponsoring these meetings, OAR will at the same time be encouraging new investigators from non-AIDS research areas to explore AIDS-related avenues of research.

Recommendation 19 [Working Group Report, p. 13, No. 2]

NIH should increase support for research of the human immune system by traditional mechanisms of investigator-initiated research and intramural projects.

Current Status

Through the definition of AIDS-related research (ARR), developed by NIAID and accepted by the OAR, NIAID has identified relevant investigator-initiated research on human immunobiology. In addition, NIAID, through the Division of Allergy, Immunology, and Transplantation (DAIT), funds a large portfolio of basic research in immunology.

NCI encourages research on the human immune system in the Division of Cancer Biology, primarily through the Biological Carcinogenesis and Cancer Immunology Branches.

NICHD supports through the R01 and R29 mechanisms a large number of grants in basic immunologic research. The Institute extensively supports R01 grants in the areas of basic developmental immunology and its role in fetal or infant susceptibility to (or protection from) HIV and investigations focused on vaginal immunology and physiology. Efforts are ongoing to aggressively increase funding available for R01 grant applications for human immune system and related research.

NIDA encourages and supports research on OIs, the neuroendocrine modulators of immune response, and basic immunomodulation in naive and addicted individuals.

Future Actions

NIH strongly agrees there is a critical need for a greater understanding of the human immune system. The scientific goals implicit in this recommendation have already been incorporated in the FY 1998 NIH Plan for HIV-Related Research. In this Plan, basic research in human immunology has been identified as the primary investment area in Etiology and Pathogenesis. Emphasis has been given to specific strategies that will encourage studies of the *in vivo* activity of the immune system, investigations to determine the life span and developmental pathways of T lymphocytes, and studies on the biology of the mucosal immune system. As an example of how the priorities set by the NIH Plan in this scientific area succeeded in shaping AIDS research, mucosal immunity became an identified critical area in which NIAID plans to stimulate research activities. The Institute specifically plans to sponsor a PA in FY 1998 on the general mechanisms of mucosal immunity with a focus on HIV/AIDS. In FY 1999, the former investment areas will become formally incorporated in the NIH Plan and will continue to be included as long as support for research of the human immune system is needed to advance AIDS research.

With the discovery that chemokine receptors act as co-receptors for HIV entry into susceptible cells, many basic non-AIDS immunologists are newly gravitating into the AIDS field. In addition, OAR will sponsor a series of workshops of expert AIDS and non-AIDS immunologists with the specific goal of accelerating progress in understanding some specific areas in immunology relevant to AIDS research. Funding opportunities will be linked to these activities as appropriate.

Overall, NIH has significantly increased support of R01 grants in the past few years, and human immunology represents a major component of these increased grants. Efforts will continue in every ICD to aggressively enhance their intramural and extramural research portfolios in human immunology.

Recommendation 20 [Working Group Report, p. 13, No. 3]

> *NIH should facilitate interactions between basic immunologists and AIDS researchers through consortial approaches. Anticipated benefits of the consortial mechanism include overcoming basic immunologists' unfamiliarity with AIDS research and concerns about working with infectious agents; facilitating the exchange of ideas, techniques, reagents, and personnel; and increasing the likelihood that postdoctoral fellows enter AIDS research.*

Current Status

Most ICDs, including NIAID, NCI, and NICHD, fund interactive research project grants (IRPGs), program projects grants (P01s), and cooperative agreements (U01s). All three of these mechanisms facilitate consortial research activities involving AIDS investigators and basic immunologists.

NIAID staff have made it a practice at all workshops to invite scientists who work in related basic areas but who are not active in HIV/AIDS research. This practice not only provides scientific context or breadth to the workshops but may permit investigators outside the HIV/AIDS field to become familiar with AIDS research.

In addition, each CFAR funds small developmental projects, open to AIDS and non-AIDS researchers, to facilitate preliminary studies. The availability of core laboratories, reagents, and technical expertise at these sites make them ideal locations for non-AIDS researchers to collaborate with AIDS investigators.

NIDA also supports meetings with participation of AIDS and non-AIDS investigators. The next meeting is planned for summer 1997, and others are being planned.

Future Actions

NIH endorses the concept that facilitating the interaction between basic immunologists and AIDS researchers could lead to new research approaches and to an increased likelihood that new investigators will enter the AIDS research arena. However, experience with some of the existing funding mechanisms, like interactive R01s and IRPGs, has not been very productive. These grant applications are reviewed by different study sections that evaluate them on an individual basis. In addition, lack of cooperation among investigators and lack of guidance on how to structure the grants are among the perceived problems. The CFARs have been very successful in promoting collaborative research. In the current recompetition for the CFARs, even greater emphasis will be given to the creation of a multidisciplinary environment for AIDS research. This is going to be

accomplished by allowing multiple institutions that contribute complementary scientific expertise to submit an application for a single CFAR award and by including the participation of multiple NIH Institutes in the PA.

NIH strongly believes that communication through participation in AIDS-related workshops and symposia is still the most effective way to foster collaborations with scientists who work in related basic fields but who are not active in HIV/AIDS research. NIH will continue and intensify efforts to provide scientific forums for exchange among AIDS and non-AIDS scientists. In FY 1997, NIAID is sponsoring a workshop at the American Association for the Advancement of Science on "Genetic Resistance to HIV-Infection," which is expected to attract participation by a number of non-AIDS immunologists.

As already mentioned, OAR will also sponsor and convene a series of workshops of expert AIDS and non-AIDS immunologists to develop a plan to accelerate progress in understanding some specific areas in immunology relevant to AIDS research. This workshop also will facilitate constructive interaction between the two groups and will foster productive collaborations.

In addition, NIH will strive with DRG to redesign the whole process of multidisciplinary grant review. Multidisciplinary approaches to scientific problems represent an emerging field not only for AIDS research. Thus, one of the challenges is to start structuring the appropriate review process for these efforts.

IV. HIV PREVENTION SCIENCE RESEARCH

Develop a comprehensive HIV Prevention Science Agenda

Recommendation 21 [Working Group Report, p. 15, No. 1]

NIH, acting through the OAR, should develop a coordinated and comprehensive Prevention Science Agenda that includes and combines biomedical, behavioral, and social interventions. This agenda should begin with an NIH-wide plan that then is integrated where possible with similar plans at the Center for Disease Control and Prevention (CDC) and other relevant Federal agencies.

Recommendation 22 [Working Group Report, p. 15, No. 2]

NIH should convene an HIV Prevention Science Advisory Committee reporting to the Director of OAR.

Recommendation 23 [Working Group Report, p. 15, No. 3]

OAR should appoint an HIV Prevention Science Coordinator charged with coordinating the implementation of the Prevention Science Agenda.

Current Status

NIH currently supports behavioral and biomedical HIV prevention activities primarily under the rubrics of Behavioral and Social Science, Natural History and Epidemiology, and Vaccine research. However, it has become increasingly apparent that there is a complementary relationship between these areas and that, in many instances, they might be combined into a more comprehensive HIV prevention approach. For example, it is important to identify and assess the behavioral factors that operate in the development, testing, and dissemination of HIV-preventive microbicides or vaccines. Similarly, it is important to ascertain the impact of behavioral interventions on disease outcomes, such as the acquisition of HIV or other sexually transmitted diseases (STDs). Although structural boundaries related to scientific discipline and training, peer review, and program definition have contributed to the segregation of biomedical and behavioral prevention approaches at the NIH, a number of emergent research questions require a more concerted, organized, and multidisciplinary strategy. NIH agrees it would benefit from the advice of individuals with expertise in both areas about how behavioral and biomedical approaches can be linked into a more comprehensive HIV prevention science agenda.

In addition to NIH, the prevention science activities of other relevant Federal agencies are identified in the 1996 Federal Biomedical and Behavioral Research Plan and Budget for HIV and AIDS. Primarily under the headings of Behavioral and Social Science and Natural History and Epidemiology, this plan highlights scientific priorities and budgetary commitments in a range of areas of HIV prevention science.

At the international level, NIH supports research on HIV and AIDS through a number of mechanisms, including FIC training programs. Also, the annual NIH Plan for HIV-Related

Research includes scientific priorities for international research. Other Federal agencies, including the U.S. Agency for International Development (USAID), through its AIDS Control and Prevention Project, and the CDC support international research in HIV prevention. NIH also provides support for regional AIDS conferences in Africa and Asia and support for other HIV/AIDS research conferences and meetings in developing countries. NIH program staff and extramural scientists, as well as those of these other Federal agencies, frequently participate in the planning and implementation of international HIV/AIDS meetings. Recently, for example, NIH and CDC cosponsored with the Canadian Public Health Association, Health Canada, and the Joint United Nations Programme on HIV/AIDS (UNAIDS), a 1-day satellite symposium on HIV Prevention at the XIth International AIDS Conference in Vancouver.

To begin addressing the range of activities recommended above, NIH has already taken the following actions:

> The OAR Behavioral and Social Science Coordinating Committee Chair has assumed the role of Prevention Science Coordinator. The Coordinator will work directly with the PSWG and others on the development and implementation of the Prevention Science Agenda and Plan.
>
> NIH has appointed an HIV PSWG, under the auspices of the OARAC. This group consists of 10 nongovernmental individuals (both scientists and community representatives) with expertise in behavioral and social science and biomedical science relevant to HIV prevention. The PSWG will consult with the OAR Director on the development of an NIH-wide prevention science plan and agenda for future research, as well as on other related matters. (The PSWG will refer in this effort to the NIH Plan for HIV-Related Research, as well as to the recommendations of the NIH AIDS Research Program Evaluation Task Force.) This group also will seek the input of NIH and other Federal agency staff, as well as other nongovernmental researchers and community representatives, on an *ad hoc* basis.

Future Actions

After developing an explicit HIV Prevention Science Plan, NIH will work with DHHS leadership to facilitate the integration of the plan into a larger HIV prevention strategy involving other relevant Federal agencies and departments.

NIH recognizes the importance of expanding international research and cooperation in HIV prevention. As a first step, the new PSWG will consider the international component of the NIH HIV Prevention Science Plan and the extent to which it can become part of a larger, international strategy. NIH will furthermore seek to explore with the White House Office of National AIDS Policy how to link the U.S. HIV prevention science efforts with those of other nations, for example, by working with UNAIDS.

The PSWG has been appointed, has met in person and by conference call, and has presented its recommendations for NIH science and funding priorities in FY 1997 to the OAR Director. Subsequent meetings are being arranged, during which the PSWG will generate ideas for the

NIH-wide HIV Prevention Science Plan, which will be developed in conjunction with the FY 1999 NIH Plan for HIV-Related Research.

Recommendation 24 [Working Group Report, p. 15, No. 4]

NIH IRGs for the review of AIDS research grants should be reconfigured to include one with appropriate expertise in and responsibility for HIV prevention science proposals (including cross-disciplinary studies).

Please refer to the NIH response to Recommendation 8.

V. CLINICAL TRIALS

Integrate all adult clinical trial programs into a single network

Recommendation 25 [Working Group Report, p. 17, No. 1]

A single integrated adult clinical trials network should be created with primary sponsorship from NIAID and ancillary funding from other Institutes involved in clinical trials.

Current Status

This recommendation is potentially the most complex of those made by the NIH AIDS Research Program Evaluation Working Group and the Clinical Trials Area Review Panel. There are a variety of views within and outside of NIH regarding specifics, but there is general agreement that appropriate, well-considered changes would be of benefit in improving the efficiency and value to the public of the NIH investment in HIV/AIDS clinical trials networks. Since both the Adult AIDS Clinical Trials Group (AACTG) and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) trials networks have recently been recompeted and the next renewal of awards is not scheduled until the year 2000 (for both programs), there is ample time for careful consideration of this recommendation and the opportunity to implement it and/or other changes (including the recommendation to develop a standard for databases for all NIH-funded HIV/AIDS clinical trials) in a coordinated fashion.

Future Actions

A committee cochaired by the Directors of OAR and NIAID with representation from OAR and involved ICDs and investigator groups will develop a proposal aimed at achieving the goal of improving the efficiency, scientific productivity, and public health relevance of the NIH-supported adult clinical trials networks. An update on the committee's activities will be presented to the OARAC and to the Directors and advisory councils of the involved ICDs by fall 1997. A draft proposal will be developed and submitted to these groups by spring 1998 for their review.

Recommendation 26 [Working Group Report, p. 18, No. 2]

A uniform standard for clinical trials databases should be developed to ensure that data can be shared between studies both within and across trials programs.

Current Status

NIH concurs with the recommendation that, in principle, uniform standards for core database standards for collection of key baseline and outcomes data should be developed and applied, whenever possible, across protocols within NIH-funded clinical trials networks. Uniform standards not only facilitate exchange of information and allow more rapid, accurate cross-study

analyses and longitudinal followup of participants, but also have the potential to improve operational effectiveness and efficiency. Currently, the two main occasions for sharing data among studies are "overview analyses" and "patient coenrollment." Overview analysis consists of pooling key baseline and outcome data from several generally similar studies for the purposes of examining the consistency of results across studies and addressing questions that require more data than any of the individual studies can provide. This process is sometimes referred to as "meta-analysis." Data sets merged in this way are usually from Phase III studies, which are larger, randomized, controlled trials with clinical endpoints.

Patient coenrollment, when a patient is enrolled in more than one study at the same time or at different times, is common among the HIV-infected population. For sequential enrollments, e.g., when a patient enrolls in an antiretroviral trial for treatment-naive persons and then later enrolls in a "salvage" protocol for initial treatment failures, data management issues are minimized if standardization of key outcome definitions has occurred. The situation is more complex when the coenrollments are contemporaneous (e.g., when a patient is enrolled in an antiretroviral trial and an OI trial at the same time), because efficiency—to eliminate repetitious forms completion and data entry—is as important as consistency.

NIH-funded clinical trials networks are working steadily toward greater standardization across trials by adopting generic (rather than study-specific) data forms wherever possible. The Pediatric ACTG (PACTG), cosponsored by NIAID and NICHD, has been successful in this regard. The difficulties are greater when collaboration involves separate clinical trials networks, such as the AACTG, the CPCRA, the Mycoses Study Group, and the National Eye Institute's (NEI) Studies of Ocular Complications of AIDS (SOCA).

Some progress in developing uniform standards has been made with regard to trials conducted by the AACTG and the CPCRA. For treatment side effects, all studies in these groups use the NIAID's Division of AIDS Table for Grading Severity of Adult Adverse Experiences. With regard to outcome data, the CPCRA led the way several years ago with adoption of detailed criteria for both confirmed diagnosis and presumptive diagnosis of each of the AIDS-related infections. The AACTG has nearly completed a similar project that was substantially based on the CPCRA criteria. Although the two sets of criteria will not match exactly, there will now be a high degree of standardization within networks that will facilitate pooling of data, even across networks.

Standardizing key baseline data for future trials should be feasible if the clinical trials networks and PIs recognize the value of delegating the authority to make these decisions to a central group, with representation from all the networks and data management centers. This would contrast with the current approach in which each network attempts to standardize key baseline and/or outcomes data separately.

Most of the concern about uniform standards focuses on randomized Phase II through Phase IV trials, where it is more likely that more than one study addressing a similar question will be compared, and for which "overview analyses" will be performed. Key baseline data should clearly describe the patient populations under study in a consistent manner so that similarities and

differences among studies can be readily ascertained and understood; otherwise, subsequent analyses and interpretations of the cross-study data will be ambiguous.

In addition, the large number of HIV-infected individuals enrolled in NIH-supported clinical trials has inadvertently created a large, continuing database of prospectively followed patients that should be assessed for the potential for conducting certain cross-protocol, epidemiologic-type analyses. While the more rigid selection criteria necessary for intention-to-treat analyses in randomized controlled trials (RCT) limit the scope of epidemiologic-type analyses that can be conducted using the cross-protocol RCT database, such analyses should be considered when appropriate. Ideally, such analyses should be conducted collaboratively with investigators involved with the AIDS cohort studies, in an effort to fully assess the limitations and applications of the findings.

Future Actions

OAR will convene a meeting of both PIs and ICD program representatives of the NIH-funded clinical trials networks to determine the extent to which standardization is feasible and appropriate and to identify a process for setting the standards. Initially, the focus of such standardization should be on demographic, clinical event, and survival data. In the event of cross-protocol RCT analyses, the NIH will encourage inclusion of cohort-based epidemiologists in the design and interpretation of findings.

Recommendation 27 [Working Group Report, p. 19, No. 3]

> *The Working Group recommends an early reexamination of the optimal approach to future pediatric AIDS clinical trials. Furthermore, significant reductions in allocations to the PACTG are recommended. These should be implemented in such a manner so that the essential clinical trials function of the PACTG is not impaired.*

Current Status

Pediatric funding for clinical trials in both NIAID and NICHD had moderate decreases during FY 1996-97. With no increase for inflation, subsequent level funding amounts to a continued funding decrease in pediatrics.

Current data indicate that at the end of 1993 there were 12,340 living children with perinatally acquired HIV infection in the United States, 56 percent of whom were under the age of 5 years (Davis, S. et al., *JAMA* 1995;274:952-5). During the ensuing 3 years, an additional 6,500 infected women have given birth annually. Although the PACTG has demonstrated with ACTG 076 that azidothymidine (AZT) can reduce the risk of perinatal HIV transmission to a baseline rate of 8 percent from 25 percent, it is unrealistic to expect that the 076 AZT regimen will be uniformly offered to and accepted by all HIV-infected pregnant women in the United States (or that it will have an efficacy equivalent to that observed in ACTG 076). Many HIV-infected women do not know their HIV infection status; a significant percent of infected women lack prenatal care and are seen for the first time either very late in pregnancy or in labor; some

infected women will refuse to take AZT; and finally, the effect of increasing AZT resistance on the regimen's efficacy is unknown. Even optimistically assuming 75 percent implementation and full efficacy of the ACTG 076 regimen, it would be anticipated that at least 750 infected children continue to be born annually and that approximately 14,000 infected children are alive in the United States as of 1996.

Therefore, there should be sufficient numbers of infected children available in the United States for the conduct of several Phase III pediatric and perinatal trials in addition to Phase I/II trials for at least the next 5 years (clinical efficacy trials in pediatrics have involved only about 800-1,000 children because of the rapid onset of symptoms in pediatric HIV infection and the use of pediatric-specific clinical endpoints such as failure to grow). Some of the critical objectives for pediatrics trials include evaluating simpler and, it is hoped, more effective methods to reduce perinatal transmission; evaluating the effect of newer potent combination antiretroviral regimens in very young perinatally infected infants as a model for therapy during primary HIV infection; assessing the impact of new drug regimens on pediatric-specific endpoints over time; and evaluating of the pharmacokinetics and safety of new antiretroviral and OI drugs in the pediatric and pregnant populations.

NCI sponsors the largest organized clinical trials network for treatment of pediatric malignancies; more than 60 percent of children with malignancies are referred to these networks for trials. While the numbers of HIV-infected children with malignancies are small, the Pediatric Oncology Group supported by NCI has established important information regarding the association of leiomyosarcoma with pediatric HIV infection and the possible etiologic role of Epstein-Barr virus (EBV) in this cancer.

Although the number of HIV-infected children is limited in comparison with infected adults, a significant portion of research on adult HIV infection is conducted outside of federally supported clinical trials networks by pharmaceutical companies or basic federally supported research conducted in separately funded epidemiologic cohorts of infected adults, such as the Multicenter AIDS Cohort Study (MACS). However, because of the limited population, most epidemiologic as well as clinical and basic research in pediatric HIV infection is conducted in the context of clinical trials funded by the PACTG.

The development and testing of pediatric drug formulations by the pharmaceutical industry often lag substantially behind those for adults, and many drugs would not be studied in a timely fashion or at all in infected children without federally sponsored clinical trials.

If the PACTG is to continue to fulfill its scientific agenda, several prerequisites must be maintained. Continued access to the infected pediatric and perinatal population is crucial. HIV infection in women and children is geographically dispersed, and increasing incidence in rural areas of the South has been observed. The recent addition by NICHD of eight trial sites to its Pediatric/Perinatal HIV Trials Network, five of which are located in the South, is important in the maintenance of access to research study patients. Adequate funding to enroll and maintain a mainly indigent population, often with social situations complicated by illegal drug use, is essential. Funding of advanced technology laboratories capable of conducting pathogenesis-based

research in the context of the trials also is critical; the NIAID PACTG recompetition will provide a more centralized group of sites with such technology.

In the future, collaboration with international sites, particularly for the conduct of perinatal trials, may be important. Perinatal prevention strategies and approaches for treatment of infection will differ in developed compared with developing countries. Collaborative perinatal and therapeutic trials of the PACTG with other developed countries (e.g., Europe and certain South American countries) may be needed as perinatal transmission diminishes in the United States over the next 5 years. Phase III trials of preventive and therapeutic approaches for the developing world are needed as well; the results of these trials will have relevance for maternal and child health worldwide.

Future Actions

NIH will continue to monitor and when appropriate modify the level of support provided to the pediatric clinical trials effort in the context of its other pediatric HIV-related activities to avoid duplication and ensure conservation of resources and the most productive use of funds. The PACTG has agreed to establish an external advisory group composed of outside experts to provide advice to the PACTG scientific leadership on the scope and directions of the pediatric clinical trials effort. In addition, interactions of the NCI-sponsored Oncology Groups with the PACTG will be facilitated to ensure maximal utilization of the HIV-infected pediatric population with therapeutic oncology trials.

It is anticipated that, over the next several years (prior to the time of PACTG refunding), the scope of the pediatric HIV epidemic and perinatal HIV transmission in the United States and in other countries will be better defined. As trends become clearer, the need for and approach to designing and conducting pediatric clinical trials will be reviewed by a panel of experts in pediatrics and maternal health, and appropriate recommendations made.

Recommendation 28 [Working Group Report, p. 19, No. 4]

An oversight committee for all NIH-sponsored AIDS clinical trials should be created that is based in the OAR and includes broad scientific and community representation.

Current Status

The NIH fully supports the goals of integration, coordination, and collaboration across the ICDs. Since the Clinical Trials Area Review Panel evaluation in 1995, these goals have begun to be accomplished with the use of several mechanisms. First, the NIAID-sponsored "Intergroup Scientific Leadership" meetings have been initiated among the scientific leadership of the adult and pediatric ACTGs, the CPCRA, and other-NIH sponsored clinical trials groups (SOCA, AIDS Malignancy Consortium [AMC], Neurologic AIDS Research Consortium [NARC]), and the leadership of NIAID and other ICDs that support HIV clinical research. The purpose of these meetings is to facilitate the development and implementation of a more unified coherent scientific agenda for NIH's HIV/AIDS clinical research networks and to optimize coordination and

communication between NIAID, other ICDs, and the NIH-sponsored HIV/AIDS clinical research networks.

Second, some of the functions of inter-Institute planning and coordination are being performed by the OAR Therapeutics Coordinating Committee, with representation from key ICDs involved in AIDS drug discovery and/or clinical trials. This committee reviews and develops recommendations to this section of the NIH Plan for HIV-Related Research annually and includes broad scientific and community representation during the final stages of development of the proposed plan. However, because its primary purpose is to act as the basis for NIH budgeting for AIDS research across the ICDs, this broad-based planning activity occurs 2 years in advance to provide adequate time for senior NIH, DHHS, and Congressional review and adjustment and is therefore general in nature.

Future Actions

OARAC will establish a Therapeutics Research Working Group to advise on the broad scientific direction, size, and scope of the NIH HIV/AIDS therapeutic research efforts, including drug discovery and development and clinical trials. This group will draw membership from nongovernmental experts. It will act to advise OAR on research in these areas and will work with the OAR Therapeutics Coordinating Committee in developing the annual NIH Plan for HIV-Related Research.

VI. DRUG DISCOVERY RESEARCH

Refocus and restructure the drug discovery research effort

Recommendation 29 [Working Group Report, p. 21, No. 1]

An external scientific advisory board, including a representative from OAR, should be constituted to provide guidance regarding appropriate goals for future DTP AIDS research activities. Future assessment of the DTP AIDS drug discovery program should include its ability to support the overall NIH drug discovery effort for HIV and for the anti-OI discovery efforts of other ICDs. NCI bears a particular responsibility for the development of novel treatments for AIDS-associated malignancies. To accomplish these goals, DTP management and structure require careful review, both to determine what can be eliminated from the AIDS drug discovery effort and to appropriately assign the funds allotted to AIDS-directed research. A substantial decrease in the size and funding of the DTP's current AIDS-related drug discovery effort is appropriate.

Current Status

The entire scope and focus of NCI's drug development program is to be reviewed by a DTP Working Group that is being assembled by the NCI's Board of Scientific Advisors for the Extramural Program. The reviewers on that panel will include experts in AIDS drug discovery and development, and concerns related to DTP management and structure will be thoroughly considered at that time. OAR will be notified of the timing and scope of these discussions.

In response to the specific concerns expressed, DTP currently is actively supporting the efforts of the other ICDs as opportunities arise. For example, NCI's databases and open compound repository have been freely available and used by NIAID in its efforts to determine potential topically active virucides. NCI has had in place a screening mechanism, described in detail below, to detect agents with selective activity in AIDS-associated lymphoma. A compound detected in this screen is currently in advanced preclinical development. NCI will continue to refine its efforts in AIDS-associated malignancy drug development as advances emerge in its understanding of the pathogenesis of these diseases.

Future Actions

In response to the recommendation for a decrease in size and funding of DTP's AIDS-related drug discovery effort, NCI has elected to cease as of January 1, 1997, all screening of natural product extracts in its primary HIV-infected cell-based screen. This contract research effort will allow redirection of approximately $1,512,000 in AIDS-related resources in FY 1997 compared with FY 1996.

The question of whether to terminate NCI's infected cell-based screen of pure synthetic compounds and defined natural product compounds is more complex, as these compounds have been submitted to NCI by academic and commercial firms from around the world with the understanding that data concerning their activity in HIV-infected cells would emerge from NCI.

Therefore, NCI will continue the cell-based screen of pure synthetic and natural product compounds until further consideration of this question by the DTP Working Group described above. It is anticipated that more directed, specific screens may be devised, based on specific molecular targets that are identified as important in the pathogenesis of HIV.

In addition, please refer to the NIH response to Recommendation 300.

VII. RESEARCH ON OPPORTUNISTIC INFECTIONS

Augment basic science research on AIDS-associated opportunistic infections and facilitate transfer of new findings to early clinical evaluation

Recommendation 30 [Working Group Report, p. 22, No. 1]

Reinvigorate the basic science research effort on AIDS-associated opportunistic infections, emphasizing studies of fundamental aspects of the biology of the responsible microorganisms and the mechanisms of disease pathogenesis.

Current Status

NIH currently supports a comprehensive portfolio of research grants, cooperative agreements, and contracts on the microorganisms associated with AIDS. NIH recognizes that there is an urgent need to strengthen the understanding of the fundamental biology and pathogenesis of HIV-related OIs. Pursuing more of the scientific research opportunities that exist will increase the critical knowledge necessary to develop methods to culture and grow these pathogens; develop improved diagnostic assays; chart the incidence, prevalence, and natural history of these pathogens in various populations; develop animal models to study disease pathogenesis; and identify new targets for therapeutics. To best accomplish these goals, NIH has incorporated the scientific goals expressed in the context of this recommendation in the 1998 NIH Plan for HIV-Related Research. In this Plan, the elucidation of the pathogenic mechanisms of HIV-related OIs has been identified as one the most pressing scientific issues to be pursued by AIDS investigators.

Specific emphases of the ongoing NIH research programs include the following:

- NIAID places a strong emphasis on basic microbiology research through the National Cooperative Drug Discovery Group for the treatment of OIs (NCDDG-OI) and through its extensive grant portfolio. Using this portfolio as a base, NIAID supports studies directed to better understanding OI pathogens and their mechanism of pathogenesis and developing improved diagnostics, drugs, and vaccines for OIs.

- NCI supports research on OIs with special emphasis on the role of viral infections in the causation of malignancies in AIDS patients. In February 1996, NCI convened the first meeting of the AIDS Malignancies Working Group to enable rapid development of tools to pursue crucial research questions in this area. This group represents a spectrum of disciplines working in relevant areas or directly with AIDS-associated malignancies. Following one of the first specific recommendations of this group, NCI developed a handbook that provides information on the current scope of NCI activities in AIDS-associated malignancies.

- NIDA supports programs that study OIs in drug users.

- NHLBI supports programs that study OIs that affect the lungs of HIV-infected individuals.

Future Actions

NIH will continue to place a high priority on research on AIDS-associated OIs. The FY 1998 NIH Plan for HIV-Related Research was developed based on these recommendations. Specific strategies in this plan are proposed that will permit a better understanding of OI pathogens and their mechanisms of pathogenesis as well as the discovery, development, and evaluation of potential regimens of agents for the prophylaxis and treatment of OIs. Special initiatives in the form of PAs and Requests for Proposals (RFPs) are planned in FY 1997 and FY 1998 to target research on one or more OI pathogens. These include the issuance in FY 1997 by NIAID of RFPs entitled "Preclinical Evaluation of Therapies for *Pneumocystis carinii*," "Preclinical Evaluation of Therapies for *Cryptosporidium parvum*," "Preclinical Evaluation of Therapies for Microsporida," and "Preclinical Evaluation of Therapies for *Mycobacterium avium*." In FY 1997, NIAID also plans to fund awards under PAs entitled "Innovative Drug Discovery Research in AIDS Opportunistic Infections" and "Collaborations for Advanced Strategies in Opportunistic Infections" to further stimulate research in this scientific area.

Special priority also will continue to be placed on tuberculosis (TB) research, and NIH will continue its collaboration with other PHS agencies in this area. NIAID maintains the Tuberculosis Working Group that serves to coordinate TB-related research within the ICD as well as to maintain collaborations with other ICDs supporting research in this area. A PA is planned for FY 1998 that would support basic and drug discovery research for AIDS-related OIs including TB and will maintain the NCDDG-OI program.

NCI held the first National Conference on AIDS-Associated Malignancies in April 1997. Important topics on the agenda concerned the role viruses play in malignancies.

OAR will convene a workshop on OIs in 1998. The goal of this workshop will be to identify specific gaps in knowledge in the field that need to be addressed and identify scientific priorities. These priorities will in turn become an integral part of the NIH Plan for HIV-Related Research in the following years.

Recommendation 31 [Working Group Report, p. 23, No. 2]

> *The NIH should pursue innovative approaches, such as enhancing the quality and AIDS focus of the Small Business Innovative Research (SBIR) grant program, to foster the transfer of new laboratory findings to early "proof of concept" clinical evaluation.*

Current Status

NIH has several programs that foster the translation of new laboratory findings into further development including both clinical evaluation and potential commercialization. These include the SBIR program, the Small Business Technology Transfer (STTR) program, and the NIAID NCDDG-OI program. Proof-of-concept testing in animal models of OIs is available through the

resources of the NIAID. Through these programs, NIH encourages interactions with the private sector and facilitates exchange of information and active interaction with clinical investigators.

The NCI Natural Products Repository is available for use in screening for novel anti-OI leads. NIH could expand the possibilities for small businesses to participate in its existing mechanisms to support and facilitate technology transfer. One approach to accomplishing this objective would be to allow the use of SBIR/STTR grants to be submitted as subprojects or cores (analytical or synthesis) for program projects and centers.

- Ten NIH Institutes and Centers have implemented a pilot "Fast-Track" mechanism to minimize the delay between Phase I and Phase II SBIRs. The Fast-Track mechanism is intended for high-quality applications with sufficient preliminary data to delineate "go – no go" milestones for the next 2 to 3 years. Reviewing Phase I/II at the same time allows awardees who successfully completed the preset milestones to proceed to Phase II. Essentially, this mechanism eliminates the funding gap between Phase I and Phase II studies and is a strong incentive for companies to apply for an SBIR grant.

- Information on the SBIR/STTR programs is now on the Internet via the NIH home page. Prospective applicants can contact the specific ICD or the main SBIR/STTR office. Many NIH Institutes and Centers already post or plan to post information about the SBIR/STTR program on their home pages.

- SBIR/STTR is now included as a support mechanism for several NIH initiatives (PAs and RFAs). The advantages are that SBIR/STTR applicants do not compete directly with R01 applicants for a limited budget. Moreover, the SBIR/STTR awards increase the funds available for a specific initiative.

- NIAID has cosponsored national SBIR/STTR workshops to specifically advertise these programs and attract the private sector; provide hands-on assistance to prospective applicants; and promote networking between the biotechnology, pharmaceutical, and academic sectors.

- NIAID has implemented an outreach seminar series to engage ACTG clinical investigators in the early phases of preclinical development. The purpose of this outreach series is to interest clinical investigators in novel therapeutic strategies/agents for collaborative pilot and clinical proof-of-concept studies.

- NIAID is convening regional and national conferences to provide advice and encouragement to small businesses and their affiliate collaborators on areas of research emphasis and strategies for preparing successful applications.

Future Actions

NIH will continue to explore innovative approaches to foster the transfer of new laboratory findings to early "proof-of-concept" clinical evaluation. The interface between early discovery and the beginnings of drug development will be supported through competitive new awards for

preclinical animal model contract drug testing facilities. In FY 1997, NIAID plans to make awards to academic institutions with expertise in animal models of *Pneumocystis carinii, Mycobacterium avium, Cryptosporidium parvum,* and Microsporida.

The SBIR and STTR Omnibus solicitations encourage research on OIs including research on new therapeutics, diagnostics, and specialized drug delivery systems. NIAID will continue to convene regional and national conferences to provide advice and encouragement to small businesses and their affiliate collaborators on areas of research emphasis and on strategies for preparing successful applications. In an effort to increase the utility of the SBIR programs to research and development firms, NIH is piloting a process of application and review designed to minimize the gap in research support between the Phase I and Phase II awards. Several ICDs, led by NIAID, announced this pilot effort in the *NIH Guide to Grants and Contracts* that incorporates innovative additions to the application requirements that are designed to facilitate the rapid transfer of research findings into further commercial development. These include a Product Development Plan and a commitment for Phase III support by a partner organization contingent upon the small business concern achieving specific technical objectives.

NIH will continue to encourage translational research and collaborations between laboratory and clinical investigators working on OIs, much in the same manner as the Strategic Program for Innovative Research on AIDS Therapies (SPIRAT) program. For example, NIAID plans to give special consideration to grant applications received in response to PA-96-069 “Collaborations for Advanced Strategies in Opportunistic Infections” that seeks to encourage “proof-of-concept” research for therapeutic and diagnostic clinical evaluations.

In keeping with the objectives and policies of the Bayh-Dole Act of 1980, the recipients of NIH research grants, contracts, and cooperative agreements are responsible for effectively and efficiently transferring technology to industry for commercial development. NIH requires notification and disclosure of inventions supported by extramural awards and may provide guidance when requested to technology transfer managers at universities and other awardee organizations. The establishment of efficient information conduits for recipients of NIH awards to develop plans and sponsored research agreements with the private sector will be facilitated through information on the World Wide Web provided by the NIH Office of Technology Transfer and OAR.

VIII. COMPLEMENTARY AND ALTERNATIVE MEDICINE RESEARCH

Strengthen the scientific base for the assessment of Complementary and Alternative Medicine (CAM) therapies for HIV disease

Recommendation 32 [Working Group Report, p. 24, No. 1]

The OAR should establish an ad hoc *advisory group to communicate community interest in the area of CAM therapies for HIV disease and to help identify therapies with apparent promise or potential danger for persons with HIV infection. This advisory group should consist of scientists experienced in clinical and laboratory evaluation of candidate therapies for HIV infection or its complications, and community representatives, including individuals who use CAM therapies.*

Current Status

The NIH AIDS research program benefits from input of scientific and community groups in its scientific planning and research efforts. The OAR will look to OAM and its Alternative Medicine Program Advisory Council for information regarding CAM therapies for HIV disease, including assistance in identifying new HIV-related CAM approaches and in providing suggested research criteria by which efficacy and effectiveness should be judged. The OAM will assist the OAR in establishing an advisory panel on CAM for HIV disease to identify and distinguish therapies with apparent promise from those with potential harm. In addition, the OAM will share its database of individuals interested in or involved with CAM treatment and research in AIDS.

Recommendation 33 [Working Group Report, p. 24, No. 2]

A catalog should be prepared of all research relating to HIV-related CAM therapies currently being supported by the NIH. OAR and its ad hoc *advisory group should work with the OAM to establish an operational definition of CAM therapy as it relates to HIV disease and to construct a taxonomy to categorize CAM therapies in this area.*

Current Status

OAM already has in its database a catalog of CAM-related information on HIV therapies supported by the NIH. A working definition of CAM is already in place as it relates to HIV disease. OAM will assist OAR in constructing a taxonomy to categorize CAM therapies in this specific area.

The OAR will confer with the OAM in the utilization of OAM's working definition of CAM and the OAM catalog of CAM-related information on HIV therapies supported by the NIH.

Recommendation 34 [Working Group Report, p. 24, No. 3]

> *The OAR and its* ad hoc *advisory group should work with the OAM to sponsor a workshop on the research methodology for the evaluation of the efficacy of CAM therapies for HIV disease. The OAR also should work with the OAM to sponsor workshops to educate individuals interested in the evaluation of candidate CAM therapies for HIV disease about the preparation of NIH grant applications and the processes by which such applications are evaluated.*

Current Status

OAM is planning several research methodology workshops. OAM will work with the OAR to sponsor a workshop in research methodology for the evaluation of the efficacy of CAM therapies and HIV disease. Similarly, OAM will work with OAR to sponsor workshops to educate individuals interested in the evaluation of submitted candidate CAM therapies for HIV disease in order that appropriate grant applications can be made to the NIH for funding of CAM research projects pertinent to AIDS.

Recognizing the mission of the OAM, the OAR has offered its assistance to the OAM leadership to hold a research methodology meeting on HIV and CAM approaches. The OAR has conveyed its interest in assisting the OAM in the planning and implementation of such a meeting, offering the involvement of OAR senior staff members, planning expertise, and resources. The OAR looks forward to working with the OAM in this effort.

Recommendation 35 [Working Group Report, p. 25, No. 4]

> *The OAR should work with the OAM and DRG to suggest individuals to serve as* ad hoc *members of IRGs that are reviewing HIV CAM therapy research proposals. Criteria for the selection of such members should include those currently utilized by DRG to select IRG members, as well as experience in the scientific evaluation of novel therapeutic approaches and knowledge of the concepts and practices of CAM therapies.*

Current Status

A database has already been established by OAM listing individuals who are willing to conduct or who have expertise in CAM research. This database will be shared with OAR for the purposes of having individuals serve in IRGs appropriate for the review of grant applications submitted to the NIH.

Since the OAR does not designate members of IRGs, the OAR will, to the extent possible and appropriate, work with the OAM in suggesting qualified people to serve on AIDS-related IRGs.

IX. REGIONAL PRIMATE RESEARCH CENTERS

Reorganize procedures to ensure that Centers are available and responsive to non-Center affiliated scientists

Recommendation 36 [Working Group Report, p. 26, No. 1]

The OAR should commission a panel to define optimal mechanisms to support AIDS research at the RPRCs and to devise strategies that permit the most promising research ideas to be tested.

Background

The NIH AIDS Research Program Evaluation Task Force Report contained several similar, recurring recommendations that relate to the RPRCs. The responses to these recommendations are consolidated and addressed below.

The network of seven RPRCs, funded by NIH through NCRR, provides basic infrastructure for nonhuman primate research. This support includes unique, specialized research facilities, scientific expertise, and veterinary staff support. The facilities and resources are shared by RPRC staff scientists and investigators from other institutions across the country. The RPRCs host investigators who receive their primary research funding from NIH, as well as investigators funded by other Federal, State, and local agencies and by research foundations or the private sector.

The RPRCs annually provide specialized resources and services for more than 1,000 investigators and house about 19,000 animals, representing a wide variety of nonhuman primate species. About one-third of all research projects conducted at the RPRCs are AIDS related. The RPRCs were instrumental in the rapid development and application of SIV infection in macaques as a model for human AIDS. The emergence of this model as a preferred animal model for AIDS pathogenesis and vaccine research has placed a strain on the limited physical resources available at the RPRCs. In response to the competition for resources, the RPRCs have implemented standardized procedures by which investigators may request the necessary resources—including laboratory space, support staff, and animals—to conduct research with nonhuman primates. These procedures have been published in the *NIH Guide for Grants and Contracts* in January 1997.

Current Status

In 1994, NCRR initiated a process to review the entire RPRC program. The purpose of this review is to define barriers to research, both administrative and physical, and to assess whether changes are needed in policy, operations, or management of the program to improve the function of the RPRCs. A portion of a Phase II study is currently ongoing with PHS set-aside funds allocated for program reviews. To complete this independent review, NCRR is submitting a request for additional support though the PHS set-aside funds for Phase II. The goal of this review process overlaps with the intent of this recommendation. An expert panel will evaluate

RPRCs, based on the information collected from the centers, and provide plans for operating the RPRCs with maximum economy and efficiency. These plans will need to balance center operational costs and per diem animal rates while meeting the future research resource needs for outstanding non-human-primate-based research.

There is no need to commission an additional panel for this purpose. The NIH AIDS Research Program Evaluation Task Force Report provides a comprehensive study of the entire NIH AIDS research program, including the role of nonhuman primates in AIDS research.

The most promising research ideas for both AIDS and non-AIDS research are selected through standard review processes for support by the appropriate ICDs. The number of PHS-supported projects at the RPRCs increased by 134 between 1990 and 1995. In FY 1995, NIH grant awards to RPRC scientists and other investigators totaled $139.7 million, of which 26.5 percent ($37 million) was awarded to RPRC staff scientists. Of the total, $49.5 million was targeted to AIDS research, and 41.5 percent of the AIDS research dollars ($20.54 million) at RPRCs was awarded to staff scientists. NCRR supports the RPRC core grant that provides the research infrastructure for some of those investigations. NCRR estimates that about $5 million to $7 million in addition was awarded to staff scientists through the RPRC's core grant (P51) for an array of biomedical research projects, including those for AIDS research. Thus, the majority of research projects at the RPRCs are supported by peer-reviewed Research Program Grants (RPGs) provided by the ICDs (including NCRR) to individual investigator-initiated projects.

Future Actions

The very limited research support provided to investigators through the RPRC core grant (P51) will be phased out and no longer be provided though that mechanism. NCRR will continue to provide grant support to each RPRC for the research infrastructure to host nonhuman primate research. Core scientists at RPRCs are being required to obtain at least 60 percent of their salary support from other sources, preferably through research grants funded by other NIH components. The success of the RPRCs and their core investigators will be evaluated on their ability to attract and maintain strong collaborations and other sources of funding for research activities.

Further removal of research dollars from the RPRCs will reduce the flexibility of the RPRCs to provide funds for pilot studies, whether or not they are initiated by RPRC-based investigators. However, competitive supplements or small grants, R03 or R21 mechanisms, can be considered in the standard review and funding cycles.

Recommendation 37 [Working Group Report, p. 26, No. 2]

The process for competition of NCRR AIDS supplemental funding should be opened up to all extramural investigators.

Current Status

Initially, some "supplemental" resources, primarily for pilot studies in AIDS research, were provided to investigators through the RPRC core grant (P51). This support mechanism was abandoned several years ago and specific AIDS-related projects have been competed at the time of RPRC review and renewal. Core scientists at RPRCs are required to obtain at least 60 percent of their salary support from other sources, preferably through research grants funded by other NIH components.

Currently, the RPRC grant (P51) includes about 5 percent of its budget to support primary research to investigators based full time at the RPRCs. This portion is not specifically designated as AIDS funding or reserved exclusively for RPRC-based investigators. In FY 1995, RPRC-based scientists accounted for about one-quarter of all PHS supported projects at the RPRCs.

Recently, an RPRC Coordinating Committee composed of representatives of each RPRC appointed by the Director of NCRR's Comparative Medicine area was established to review and coordinate access for investigators across the network of RPRCs, set standards for research reagents, identify RPRC program needs, and identify areas of collaboration.

Future Actions

NCRR has recently developed a program to further enhance access to the RPRCs for scientists from other research organizations and also to provide an incentive for staff scientists at the RPRCs to collaborate with non-Center associated scientists. This program will be initiated in FY 1997. To be eligible, a collaborative investigator (not at an RPRC) must develop a consortium arrangement with an appropriate RPRC-based scientist. A PA describing this new program was published in the *NIH Guide for Grants and Contracts* in January 1997. The OAR has provided seed funds ($2.5 million) to RPRCs for AIDS research, and NCRR will contribute a modest level of funds to this effort for non-AIDS research. Hence, this new approach will stimulate both collaborative research and access to the RPRCs, two actions recurrently recommended in the Task Force report.

The RPG applications submitted in response to this PA will be assigned by the Office of Referral of the DRG to either DRG study sections or to Institute/Center IRGs with appropriate scientific expertise. It is anticipated that this approach will enhance access to the RPRCs and also provide an incentive for staff scientists to collaborate with non-Center-associated scientists.

Recommendation 38 [Working Group Report, p. 27, No. 3]

> *To optimize the quality and productivity of AIDS research conducted at the RPRCs, the NCRR IRGs that review the Centers should be strengthened by the addition of scientists with expertise in AIDS and AIDS-related research.*

Current Status

NCRR fully recognizes that this was an issue in the past. The Scientific Review Administrator of the NCRR Comparative Medicine IRG for the past few years has vigorously recruited reviewers from the field who are experts in the AIDS research arena to provide adequate expertise in AIDS subject areas. This IRG now has reviewers who are experts in AIDS research, many of whom have also served on the regular AIDS IRGs in the DRG. Almost all investigator-initiated project grants in AIDS research at the RPRCs are referred by DRG to appropriate IRGs either within the DRG or within Institutes/Centers, based on expertise within the IRGs. Only a few (less than 10) were funded by NCRR after review by the NCRR Comparative Medicine IRG.

Future Actions

NCRR will continue to monitor the reviews of the Comparative Medicine IRG to ensure that adequate expertise for AIDS topic areas is incorporated in the review process.

Recommendation 39 [Working Group Report, p. 27, No 4]

> *Open competition for funds to support relevant animal costs included in DRG-reviewed grants might be accomplished through a regularly recurring RFA.*

Current Status

This recommendation raises two issues. One is a cost-containment issue for animal research in general. The second is the availability of adequate animal resources, particularly nonhuman primates, in a timely fashion and commensurate with project development. These issues have arisen primarily because cost-containment efforts of the IRGs permit only restricted numbers of animals for vaccine studies or other research projects that might benefit scientifically from larger numbers of animals in individual study groups.

About half of all NIH-funded research project grants include animal-related research. Animal-based research costs should be appropriately requested and justified in conjunction with investigator-initiated RPG applications. The review of requests for animal per diem costs is considered as part of the critique of RPG applications by IRGs. It would be neither practical nor efficient to independently review requests for animal per diem costs through a separate, recurring RFA that is not directly linked to research proposals. Those per diem charges, just as any laboratory-based research costs, are appropriately included in research funds provided to grantees through their research project grant awards.

Future Actions

NCRR has convened an expert committee to examine approaches to contain per diem costs for all animal-based biomedical research supported by the NIH. The report from this committee will be available in spring 1997.

Where projects involve high levels of animal research costs associated with nonhuman primate studies, an alternative approach is to provide resources in a timely fashion. Milestones for additional funding could be proposed by the investigators at the time of application or negotiated after DRG review with program staff for ICD funding. For example, this approach might be considered for applications in which inadequate preclinical, small animal studies are presented as preliminary data and it is apparent that nonhuman primate studies will be delayed.

X. AIDS RESEARCH CENTERS

Strengthen AIDS Research Centers to promote multidisciplinary research on the disease

Recommendation 40 [Working Group Report, p. 28, No. 1]

The Working Group recommends that funding for the CFAR program as a whole be increased by approximately 50 percent. This would allow annual funding in the range of $750,000 to $1.5 million per year, to be allocated in proportion to a Center's research capacity and its ability to build an interdisciplinary research program and attract R01s.

Current Status

NIAID agrees that increased funding for some CFAR sites with particularly strong and well-integrated programs would be productive and important. A request to OAR to increase the total level of funding for the program has been included in the budget submissions for FY 1998. Programmatic changes designed to increase the responsiveness of the CFARs to the greater scientific community have been approved, in concept, by the NIAID's ARAC and are being implemented. These changes include modifications to the number and focus of required cores (basic, clinical, and developmental cores) and a "rolling" competition in which several new and recompeting CFARs apply for renewal or new funding each year (rather than the entire program turning over once every 5 years). These changes are designed to provide maximum flexibility to institutions seeking funding as a Center and increase opportunities for funding. In addition, each institution is encouraged to build on its unique scientific strengths in designing its CFAR application. NCI, NHLBI, NICHD, NIDA, and NIMH have expressed interest in cosponsoring with NIAID the CFAR program.

Future Actions

An initiative is planned for FY 1998 to begin funding CFARs on the "rolling" competition basis. Funding levels will be determined by peer review, which will consider each applicant institution's level of AIDS-related research support and other factors.

Recommendation 41 [Working Group Report, p. 29, No. 2]

The comprehensive research centers program, funded by NIMH, has been found to be productive and should be maintained.

Current Status

The NIMH AIDS Research Centers PA was issued in 1985 (jointly with NIDA); the first two Centers were supported in 1986. This mechanism was instrumental in jump-starting a field of research and mounting a public health response to the emerging but little understood epidemic. This network of interdisciplinary scientists was critical in translating behavioral research findings

to the biomedical community and public and providing national and international leadership in primary and secondary AIDS prevention.

NIMH AIDS Centers maximize opportunities to pursue cross-disciplinary research. Because Center studies can be organized in parallel with one another, the findings can be compared. In its evaluation of the NIMH portfolio, the IOM report stated that "One creative mechanism that has been developed to foster collaboration is the multidisciplinary AIDS research centers. Much of the needed behavioral and social research on AIDS prevention requires large, multidisciplinary teams of scientists with close working relationships with many of the different communities in which interventions must be conducted."

Currently, five NIMH AIDS Research Centers are being supported, which constitutes 15 percent to 19 percent of the NIMH AIDS budget. Four Centers include cores and R01 type projects; the latest Center to be supported is under a CFAR stimulated by the joint NIAID/NIMH RFA. The Centers have developed in response to the changing epidemiology of HIV-infection and scientific developments. The initial Centers had a broad commitment to AIDS prevention that applied principles from behavioral medicine to this behaviorally mediated disease. When it became apparent that the virus affected the central nervous system (CNS), two Centers emerged to study the neurobehavioral consequences of HIV infection; one used a serodated cohort and another focused on the basic science of AIDS dementia. The Centers have become a magnet for other Federal and private funding; for example, one Research Center currently receives only 38 percent of its support from NIMH.

NIMH staff provides guidance on the scope, theme, and priority for new Center proposals. In the past 2 years, the establishment of priority and relevance for this technical assistance has been consistent with the NIH Plan for HIV-Related Research and OAR guidelines. Institute program staff also counsel investigators to explore other mechanisms that may be more appropriate for their research aims. For example, a Program Project or Interactive R01s may be a better match that maintains a balance among the mechanisms.

Future Actions

NIMH concurs with the recommendation that the AIDS Research Center program should be maintained. As the research base has expanded, however, there is a need to refine the NIMH centers concept. NIMH is implementing some new strategies to ensure that Centers continue to be cost-effective, of high scientific merit, and consistent with the needs of a maturing field. Peer review is used to critique the scientific merit of supplemental requests and renewals and to assess components of Centers that are not productive.

To stimulate innovation and to contain costs, NIMH is in the process of disaggregating some of the outstanding research projects to R01s. Two research projects at the San Francisco center have been converted to R01s. These converted grants will continue to relate to the Center and enhance the research productivity of high scientific merit. The Center will provide infrastructure and multidisciplinary expertise to its projects and R01s. NIMH staff is planning an extensive discussion with its Advisory Council and five Center Directors in May about the most efficient way to accomplish this goal without disrupting critical AIDS behavioral research.

XI. REPOSITORIES AND DATABASES

Ensure that central repositories of biomedical specimens and databases are of the highest quality and accessible to qualified investigators

Recommendation 42 [Working Group Report, p. 30, No. 1]

Improvements should be made in repositories and databases in accord with three principles: repositories and databases should be investigator-designed and hypothesis-driven; accessible to all qualified investigators; and coordinated under a new user-friendly central tracking system maintained under the auspices of the OAR. Support should be provided for collection of specimens, as dictated by scientific needs, and for these repositories and databases.

Recommendation 42, Part A

Repositories and databases should be investigator-designed and hypothesis-driven.

Current Status

NIH concurs with the recommendation that repositories and databases should be scientifically designed and the specimens and data collected should be available to test specific scientific hypotheses. Central specimen repositories for samples collected by investigators from participants in NIH-sponsored HIV-related multicenter observational cohort studies and/or treatment-related initiatives are maintained at a number of ICDs, including NIAID, NHLBI, NIMH, and NCI. Specimens stored in these central repositories are linked to clinical data and represent a key national resource for crosscutting, epidemiologically based, and clinically based laboratory investigations. Investigators at the sites where the specimens and relevant data are collected are chosen as a result of rigorous peer-review processes. These investigators actively participate in the processes of designing the databases with which the specimens are linked, deciding what specimens are collected and stored, and deciding the particular manner in which specimens are stored.

The collection and storage of certain specimens, particularly those difficult, inconvenient, or costly to obtain (e.g., semen, lymphoid tissue, and fecal matter), are performed on the basis of certain, specific hypotheses. Other, more readily obtainable specimens (e.g., serum, plasma, and frozen cells) are not necessarily distributed on the basis of specific hypotheses, but are distributed to those scientists with specific hypotheses to test.

In addition to central, national specimen repositories, many institutions participating in HIV-related epidemiologic cohort studies or clinical trials maintain local repositories of biological specimens obtained from study participants at that particular site and linked to the clinical and epidemiologic data obtained and stored at that site. Some of these specimens and data are collected in an effort to address specific scientific hypotheses, while some are collected to serve as a resource to address future hypotheses that may not be developed at the time of collection.

NIAID also maintains the AIDS Research and Reference Reagent Program, through which renewable specimens such as virus stocks and monoclonal antibodies are made available to the scientific community. The repository exists to supply the necessary reagents to assist investigators in addressing specific scientific hypotheses.

NIH also supports HIV-related studies that collect and analyze data without linkage to biological specimens. For example, NIMH, NICHD, NIDA, NIAAA, NIAID, NHLBI, and other ICDs support research on behaviors and behavior change related to prevention of HIV infection. Much of this research is supported through investigator-initiated, peer-reviewed grants; cooperative agreements and contracts also are sometimes used to support data collection in behavioral research. Peer review normally ensures that data collection undertaken as part of these studies is hypothesis driven. Occasionally, studies may be designed to address hypotheses deriving from several theoretical paradigms, especially when large representative population-based samples are needed.

Future Actions

NIH will continue to ensure that repositories and databases are scientifically designed and that the data and specimens collected are made available to test specific scientific hypotheses.

Recommendation 42, Part B

Repositories and databases should be accessible to all qualified investigators.

Current Status

NIH concurs that repositories and databases should be more widely accessible to all qualified investigators. NIH has a major responsibility in ensuring that repository specimens are protected as a national resource for use in research studies of the highest scientific merit.

NIAID and NHLBI have established review mechanisms for collaborators seeking access to the repositories and databases associated with studies funded by the ICDs. These review mechanisms were established in collaboration with the investigators from the research institutions where these studies are based—institutions which represent the actual owners of the clinical specimens and the data to which these specimens are linked. The terms under which these studies are funded specifically and explicitly state the need for sharing the specimens and data through collaborations with “outside” investigators (i.e., qualified investigators not directly associated with the study in question). Requests for collaborations are evaluated for scientific merit in a timely fashion by each of the funded groups of investigators along with a representative or representatives from ICD program staff. Decisions as to whether or not to proceed with collaboration requests are based upon the scientific merit of the proposals, the proven expertise of the requestors to perform the work being proposed, the availability of specimens to perform the work being proposed, and the possible redundancy of the investigations in view of the ongoing work by members of the relevant studies or by collaborators with prior approval to perform the studies in question.

NIAID has distributed its *Procedures for Establishing Collaborations to Access Specimens from DAIDS-Sponsored Repositories* widely within the research community. The guidelines will soon be available at the NIAID home page of the NIH World Wide Web site. The NIAID Research and Reference Reagent Program specimens and reagents are available to all qualified investigators. The NHLBI Repository also will be available in the next several months on the NIH Web site.

Current practices do not require access to all stand-alone databases supported by NIH funds. Many multisite networks collecting data under cooperative agreements include data coordinating centers that provide and manage access to data according to principles decided by the network.

In some cases, data are proactively archived and disseminated in the form of "public use" data files for use by other researchers. In other cases, data are shared by investigators in response to specific requests from outside researchers. In many cases, funded investigators may decline to share data, either during the first few years of data analysis or indefinitely. Legal issues limit the extent to which NIH may require that all data be made accessible, while ethical concerns regarding the protection of confidentiality may limit the extent and form of data access investigators can provide. Where ethical considerations are pertinent, the development of procedures for providing access to data under secure contractual arrangements that provide for the protection of human subjects has proven to be both feasible and beneficial. However, experience at NIH with such arrangements is scattered, and both the acceptability and effectiveness of data-sharing models would be improved by a sharing of experiences among relevant ICDs.

Future Actions

NIAID will make available to the OAR copies of the Repositories Procedures in both hard copy and electronic formats. OAR will distribute these Repository Procedures to all ICDs sponsoring HIV-related studies that maintain data and/or collect specimens of value to the general scientific community. Relevant ICDs will be encouraged to use these Repository Procedures as a model to develop their own guidelines that address the specific needs and constraints of the studies they support.

NIH will establish a working group to share experience with and assess models for providing access to stand-alone databases collected with NIH support. The group should be responsible for developing guidelines and recommendations regarding data sharing that take into account legal constraints and ethical issues such as human subjects protections. The working group should be led by staff from OAR and Office of Extramural Research (OER). Guidelines should be developed with input from the NIH Office for Protection from Research Risks (OPRR), the NIH Office of the General Counsel (OGC), the DHHS Data Council, and NIH and nongovernmental researchers representing scientific disciplines that vary in current practice regarding data sharing. Guidelines should encourage the development and review of data access plans when the study is being developed.

Recommendation 42, Part C

Repositories and databases should be coordinated under a new user-friendly central tracking system maintained under the auspices of the OAR.

Current Status

NIH concurs with the recommendation that mechanisms need to be developed which will improve the ability of investigators to assess what data and biological samples collected from federally funded, behavioral, epidemiologic, and clinical HIV studies may be available for them to address specific research questions.

The specimens maintained and distributed at various HIV-related specimen repositories are linked to clinical data at the data centers for each of the respective contributing epidemiological, treatment, and vaccine studies. Some of these data centers also are integrated into the inventory data maintained at the central repository, allowing each specific study to inventory the availability of samples when planning its own investigation or when evaluating the feasibility of a proposed collaboration. Some study data centers are not integrated into the repository database in this manner.

It would prove difficult, if not impossible, to combine the massive amount of data linked to biological specimens from the wide variety of extant studies into a single database, even at the level of an individual ICD. Moreover, even if it were possible to create such a database, it likely would not serve the goals of furthering the appropriate scientific utilization of these specimens, as the specimens and data are owned by the academic institutes funded to perform these studies, and use of these specimens and data would require the approval of the appropriate collaboration review boards of these studies.

It may be extremely useful for the OAR to maintain a list of all the NIH-funded HIV research projects that collect specimens and bank them in repositories, along with a general description of the nature of the study, e.g., descriptions of the observational cohort, the clinical trial, and its primary goals; the location of the central and/or local repository; the types of specimens collected and the schedule of the collection; and the presence or absence of mechanisms for non-study-investigators to access the specimens and the linked clinical data. OAR should be provided with blank collaboration request forms and should distribute these forms along with the name and phone number of the appropriate ICD Program Director, who will collect the completed forms and answer questions concerning access to the specific data and specimens.

Although isolated and limited efforts currently exist to track, collect, and archive stand-alone databases relevant to AIDS research, centrally coordinated information about available databases and archives does not currently exist within the NIH. It would be useful for OAR to maintain an inventory of such databases and archives that have been made accessible to nongovernmental investigators. The inventory should contain, minimally, an abstract describing the database and contact information. Ideally, it should be searchable on key words and integrated with the inventory of repositories described above.

Future Actions

ICDs that maintain specimen repositories will provide to the OAR a general description of the studies in which such specimens are collected that includes a listing of the types of specimens available, as described above. This information will be used by OAR to make the availability of biological specimens more widely known.

Similarly, ICDs that support collection of databases that have been made accessible to nongovernmental researchers should provide OAR the necessary information for the inventory. Information should be provided in a standard format in electronic form and include brief summary information about the structure and content of the database, the purposes of the study, the sample designed, and the procedures for accessing the data. OAR should make this information available through the Internet or other electronic means. OAR should (1) pilot the development of this database in a format that will create minimal burden for investigators and ICD staff but will provide a user-friendly and effective resource for scientists, (2) develop the full database, and (3) maintain it and update it periodically.

Active distribution of this information by OAR to the broader scientific community should be performed in a judicious fashion and in a manner that does not raise false expectations of unlimited and unconditional access to specimens and data. The biological specimens placed in various NIH AIDS specimen repositories are not replaceable, and care is taken by the investigators who collect and ultimately own these specimens to prevent their depletion through use in studies that represent less than critical, cutting-edge science. OAR, when communicating the availability of these specimens more widely, must inform all potential collaborators of the need to present the formal request for specimens and data directly to the responsible ICD in a manner based upon a carefully conceived and hypothesis-driven research plan, of the need for collaborating with those who collected the specimens and who maintain the data to which these specimens are linked, and of the possibility that requests may not be fulfilled. Similarly, OAR must convey the potential existence of ethical and legal restrictions on the availability and use of stand-alone databases.

XII. AIDS RESEARCH INFORMATION SYSTEM

Upgrade the NIH AIDS Research Information System and increase the information base

Recommendation 43 [Working Group Report, p. 31, No. 1]

A new information database system should be developed containing grant, contract, or intramural project titles and numbers; names of principal investigator and institutional affiliations; budget amounts; funding ICDs; and an abstract for each proposal. In addition, the Working Group recommends that a yearly summary abstract of ongoing activities and list of publications resulting from each award be prepared by the principal investigator and included in the database. The database should contain this information for every project coded by the ICDs as AIDS or AIDS-related.

Current Status

NIH concurs with the recommendation that a new information database should be developed on all NIH AIDS research awards. The OAR ARIS was developed in 1989 in response to demands from Congress, the DHHS, and the Office of Management and Budget. Since AIDS research is sponsored by all NIH ICDs, it was not possible before the ARIS was developed to rapidly and completely answer questions as to how and where AIDS research funds were spent.

Since the ARIS became operational, it has provided budgetary information necessary to track how NIH AIDS research funds are being spent. ARIS was specifically designed to report NIH AIDS dollars as they are spent under a series of established categories, i.e., Functional Categories, Special Interest Categories, and NIH Strategic Plan categories. ARIS also was designed to tracks these funds by their funding mechanism and sponsoring ICD as well as by the institution receiving the funds. At the time it was developed, ARIS was not intended to categorize or track the scientific value or progress of NIH-funded AIDS research.

Currently, the ARIS receives data from four sources. The Strategic Plan categories are established each fiscal year by the OAR Coordinating Committees. The ICDs code each research project according to the Strategic Plan categories, attach a dollar amount to each code, and submit the information directly to the ARIS. Additionally, ARIS obtains information indirectly from the DRG IMPAC system, which includes administrative and financial information about each research grant, and the DRG CRISP system, which includes the abstracts of funded projects as written at the time of application for funding. Since CRISP abstracts are written before the research is actually funded, they do not continue to reflect the scope of the research as it evolves and are not useful for linking expenditures, projects, and science.

Even apart from the problem of tracking science within a fiscal database, there are inherent problems with ARIS, such as the coding of AIDS research projects. For instance, new codes appear as AIDS research evolves and new priorities are established, making historical analysis and tracking of AIDS projects extremely difficult. Furthermore, Strategic Plan codes are not necessarily mutually exclusive, creating imprecision in reporting funds devoted to a particular area

of research. Finally, there currently is not an NIH standard definition of AIDS-related research, further complicating tracking of research among the ICDs.

Timeliness of data submission is another factor that affects the usefulness of the ARIS system. The burden of categorizing AIDS research funds falls on the ICDs at a time when staff downsizing is a reality. As a result, it has become increasingly difficult to collect the data required to maintain the ARIS database. Timeliness is particularly difficult with regard to data submissions on intramural AIDS research projects, as the cost-accounting methods and timelines applied to extramural research are not applied consistently to intramural research.

The problems outlined above occur within all NIH-wide databases. The ARIS, however, stands alone in its completeness of financial information: all NIH-funded AIDS research dollars are recorded in the ARIS as they have been since FY 1989, and these dollars agree with each ICD's appropriated AIDS funds.

The user-friendliness of the ARIS has been the topic of much debate. The developers of the system have emphasized flexibility, reliability, and integrity in order to respond to complex requests. In providing high-level searching and reporting capabilities, the ARIS has a certain complexity that makes it less user-friendly. To compensate for the natural limitations of the ARIS, its developers have worked closely with those seeking information and conducted most searches in-house, making the output available by fax, by e-mail (Internet), or on diskette.

An ARIS Enhancement Committee has been formed within OAR to identify and implement interim improvements that can be made to enhance the value and accessibility of the current database system. This committee has established contact with administrative and technical experts from the Division of Computer Research and Technology (DCRT), DRG, OER, and NIAID. Information scientists at the National Library of Medicine have also agreed to provide guidance. Through efforts to date, a prototype of a user-friendly, Web-based interface to the ARIS database has been developed. The resulting information system can search and display all the financial and coding information in ARIS as well as text descriptions of funded AIDS research projects. The project descriptions searchable through this system currently are abstracts available from the CRISP database; however, the prototype system could be easily modified to search and display other text information should it be made available to the OAR in electronic form.

Future Actions

NIH will develop a new information database on all NIH AIDS research awards. The database should include a yearly abstract summary of ongoing activities. In August 1995, the OER instituted a long-range, cross-NIH project to collect research project information through the World Wide Web. OAR is working with OER to develop and test a prototype system that would collect descriptions of ongoing research efforts as well as journal citations that arise from these efforts. Once completed, this system could be linked to the ARIS so that, when a project is selected, its matching description and citations can be easily obtained. OAR will initiate discussions with the NIH Office of Intramural Research to discuss how a similar system could be used to collect the annual reports filed by intramural scientists who conduct AIDS-related research.

Progress reports submitted for noncompetitive renewals of grants would be the best source of information on the progress of the project and timely information on scientific findings. Tracking science within the current ARIS structure by electronically appending all or part of the progress reports to the project information and Strategic Plan codes would be desirable. However, since progress reports contain proprietary information including findings contained in applications under peer review, at a minimum encryption/password schemes would need to be developed to protect the confidentiality of that information. ICDs and OER are currently working on new electronic approaches to follow noncompetitive renewals.

A key step in the new or modified ARIS will be to improve the acquisition of the data and content (e.g., complete and useful progress reports) from the grantees, contractors, and intramural researchers. Improvements in this area may include (1) linking ARIS to the developing IMPAC-2 system or (2) developing guidelines and incentives for submitting accurate, complete, and timely information that would be integrated into NIH funding requirements and disseminated to all current and potential recipients of NIH research funding.

NIH recognizes that substantial and very rapid progress is being made in the informatics community that can be expected to offer a variety of options for improving user access to ARIS. The OAR and its ARIS Enhancement Committee will continue to consult administrative and technical experts at the NIH to utilize these advancements in further developing the user-friendly prototype system for accessing the ARIS information and other pertinent information on NIH AIDS research projects. This committee will investigate all technical options, such as those which involve new Internet and Web-based client-server tools that may serve as a more user-friendly front-end to the existing ARIS, off-the-shelf commercial products that may be substituted for the present database management and retrieval system, customized upgrades of one or more components of the present ARIS, or some combination thereof.

XIII. DEFINITIONS OF AIDS AND AIDS-RELATED RESEARCH

Develop and implement a clear definition of AIDS and AIDS-related research through an evolving process

Recommendation 44 [Working Group Report, p. 33, No. 1]

The Working Group has determined that a substantial proportion of NIH AIDS funds has been previously and is presently inappropriately classified as AIDS or AIDS-related by many ICDs. Such funds should be redirected to research programs appropriately classified as AIDS and AIDS-related. It is recognized that an orderly plan for redirection is needed and that its implementation may require a period of time.

Recommendation 45 [Working Group Report, p. 33, No. 2]

The Working Group strongly recommends that the OAR, in cooperation with the ICDs, develop guidelines/criteria for the classification and coding of projects as AIDS and AIDS-related. Such a coding system should be implemented immediately to permit multiyear analyses of projects by these categories. The Working Group recognizes that these guidelines may evolve as AIDS research priorities change. It is crucial that this coding system be developed to ensure that AIDS research funds are effectively, efficiently, and optimally utilized.

Current Status

NIH concurs with the recommendation that a definition of AIDS-related research that will evolve in response to scientific priorities and opportunities is clearly needed. OAR in conjunction with the OAR Coordinating Committees and ICDs annually develops the comprehensive NIH Plan for HIV-Related Research based on the state of the science. This developmental process also includes major input from and prioritization by representatives from academia, industry, and community constituency groups who attend an annual workshop. The Plan presents the future directions and goals of the NIH AIDS biomedical and behavioral research efforts and implicitly articulates the definition of AIDS-related research.

As the planning process has responded to evolving research opportunities and new priorities have been established, NIH has already redirected AIDS funds accordingly. For instance, funds have been redirected from research projects on blood substitutes and drug screening programs. Similarly, drug development programs that had little or no relevance to AIDS research are no longer being supported with AIDS funds.

Future Actions

Beginning in FY 1999, the NIH will use the annual Plan for HIV-Related Research as the formal definition of what constitutes AIDS research. The ICDs will use this definition in coding and reporting their AIDS-related programs and projects. The implementation of the newly developed IMPAC-2 information database by the OER and the DCRT will permit an improved tracking and monitoring of NIH-sponsored AIDS research projects. Similarly, IMPAC-2 will permit ICDs to

more appropriately code these projects according to the annual NIH AIDS research plan and permit OAR to monitor project coding.

Recommendation 46 [Working Group Report, p. 34, No. 3]

> *AIDS funds should continue to support excellent work in selected underdeveloped areas of basic research judged to be likely to make substantial contributions to progress against this disease and its sequelae. The research areas for potential investment should be clearly identified in the annual NIH Plan for HIV-Related Research so that they can be targeted for NIH-wide additional support.*

Current Status

OAR concurs with the recommendation that research areas for potential investment should be clearly identified in the annual NIH Plan for HIV-Related Research. NIH recognizes the critical importance of funding for basic biomedical and behavioral research as the findings from these studies provide the foundation for the development of potential therapies, vaccines, and behavioral interventions. Beginning with the development of the FY 1998 NIH Plan for HIV-Related Research, specific targeted areas of basic research designated as "investment areas" were identified by the OAR Coordinating Committees. These investment areas are clearly identified in this plan under specific objectives within appropriate areas of emphasis. The ICDs have been informed of the goal and purpose of these investment areas and will identify programs/projects when appropriate under this new category. Projects categorized as falling under an investment area will be provided Strategic Plan codes by the ICDs so as to permit their rapid identification and tracking apart from AIDS-related research programs/projects.

Future Actions

Beginning with the development of the FY 1999 Plan, the OAR Director and the OAR Coordinating Committees may identify basic biomedical and behavioral research areas where support with AIDS funds are deemed appropriate to further advance the overall AIDS research effort. Such targeted areas will be identified as specific strategies under objectives within each area of emphasis.

XIV. OFFICE OF AIDS RESEARCH

Preserve a strong OAR to provide leadership and coordination to the entire NIH AIDS research program

Recommendation 47 [Working Group Report, p. 35, No. 1]

The OAR should immediately develop a plan to implement the recommendations in this evaluation report.

Current Status

Since the release of the Working Group component of the NIH AIDS Research Program Evaluation Task Force Report in March 1996, a series of meetings was held with the NIH Director and OAR Director and selected ICD Directors to address the implementation of many of the recommendations in this portion of the report. In August 1996, the OAR Director began developing the "Implementation Plan" for the Working Group recommendations that were not previously addressed as well as those in the individual Area Review Panel reports. The overall goal was to develop a plan and timeline for implementation of the recommendations and to provide them to Dr. Harold Varmus, Dr. William Paul, and the ICD Directors and subsequently present them to the OARAC.

These recommendations were in three general categories: cross-ICD, ICD-specific, and OAR-specific. Seven implementation groups were established with members appointed by appropriate ICDs and charged with the responsibility of developing responses to the cross-ICD recommendations. The seven implementation groups were (1) Etiology and Pathogenesis, (2) Drug Discovery, (3) Clinical Trials, (4) Vaccines, (5) Prevention Research, (6) Primate Centers/AIDS Centers, and (7) Databases and Repositories.

ICD-specific recommendations were provided to the ICDs, which in conjunction with the OAR have developed responses to these recommendations. At the same time, responses to OAR-specific recommendations were developed by the OAR.

The draft document developed through this process was provided to all of the ICDs so that their input and comments could be incorporated into the Implementation Plan that was reviewed in February 1997 by Drs. Varmus and Paul and the ICD Directors. The Implementation Plan prepared by the ICDs and OAR was presented to the OARAC in March 1997.

Future Actions

The ICDs and the OAR will continue to implement the recommendations throughout the current fiscal year and also incorporate the Implementation Plan into the development of the FY 1999 NIH Plan for HIV-Related Research. OAR will continue to closely track the ICDs' efforts in implementing these efforts.

Natural History, Epidemiology, and Prevention Research Area Review Panel Recommendations

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Recommendation 48 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 2, No. 1]

Develop an HIV Prevention Science Strategy for the National Institutes of Health (NIH), coordinated by the Office of AIDS Research (OAR).

Recommendation 49 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 2, No. 2]

Integrate the NIH HIV Prevention Science Strategy into a U.S. Prevention Plan coordinated by the Department of Health and Human Services (DHHS) and involving all relevant Agencies and Departments.

Recommendation 50 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 2, No. 3]

Take an active role in designing a comprehensive International Prevention Science Agenda that builds on the U.S. Prevention Plan and provides for the financial support and scientific expertise necessary to meet challenges in HIV/AIDS research at the international level.

Please refer to the NIH response to Recommendations 21–23.

Recommendation 51 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 3, No. 4]

Define how mucosal HIV shedding and transmission are influenced by factors such as viral subtype, local immune responses, cervical ectopy in adolescent and young women, HIV infection stage, antiretroviral treatment, and vaccines.

Current Status

The NIH portfolio in the area of mucosal HIV shedding and transmission is supported by a broad base of investigator-initiated research grants. Longitudinal cohort studies such as the Women's Interagency HIV Study (WIHS), the Woman and Infant Transmission Study (WITS), and the HIVNET constitute a major resource for pathogenesis studies, as do international cohort studies. For example, cohort studies in Thailand and India are helping understand how HIV shedding and transmission are influenced by viral subtypes that are not endemic in the United States. The Adolescent Medicine HIV/AIDS Research Network, supported by multiple Institutes, is investigating these issues in a cohort of adolescents who were infected though sexual transmission. The ICDs' portfolios are monitored continually (relative to the state of the science) to ensure that current scientific priorities are adequately addressed. In 1994, NICHD issued two RFAs, one on vaginal immunology and one on vaginal physiology, to fund more investigator-initiated research to better understand the interaction between intravaginal products and the vaginal environment. In February 1997, NICHD also sponsored a conference on the reproductive tract and HIV transmission. Areas deserving special emphasis are targeted for investigators through PAs, RFAs, or RFPs. For example, the "Mechanisms of AIDS Pathogenesis" RFA was

issued in 1995 to stimulate research on the pathogenesis of sexual/mucosal transmission of HIV or SIV.

Future Actions

NIH will continue to monitor the ICDs' portfolios to ensure that (1) the research areas of mucosal shedding and transmission are being addressed adequately, (2) specimens and data from longitudinal cohort studies are available to independent investigators studying mucosal shedding and transmission, and (3) the HIV Genetic/Antigenic Variation initiative will include a focus on viral isolates from recent seroconvertors in the HIVNET. NIH also will foster further research to define viral sequences and phenotypes over time from pairs of individuals known to be linked by sexual or perinatal transmission.

Recommendation 52 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 3, No. 5]

Conduct interdisciplinary prevention trials of the full range of promising biomedical and social and behavioral interventions to prevent HIV transmission. For example, evaluate topical microbicides, investigate new approaches to improve the effectiveness of syringe- and needle-exchange and other methods of distributing sterile syringes and needles, and evaluate a full range of approaches to preventing perinatal transmission, such as chemoprophylaxis and immunoprophylaxis as well as low-cost alternatives such as intrapartum antisepsis and nutritional supplementation.

Current Status

NIH conducts domestic and international interdisciplinary HIV prevention trials of biomedical and behavioral interventions through investigator-initiated R01s, the NIAID HIVNET, the NIMH Multisite HIV Prevention Trial, and the NIDA Cooperative Agreement for AIDS Community-Based Outreach/Intervention Research.

Ongoing prevention studies include the following:

- Screening of new compounds as potential topical microbicides by efficacy trials of two nonoxynol-9 containing formulations
- Phase I safety studies of new topical microbicides
- Efficacy studies of synthetic male condoms
- Community trials of STD prophylaxis for reducing HIV transmission
- Operational studies of needle exchange programs
- Efficacy trials of hyperimmune HIV immunoglobulin (HIVIG) for the prevention of maternal-fetal HIV transmission

- Studies of the possible benefits of nutritional supplementation (including vitamin A) in reducing maternal-fetal HIV transmission

- Phase I studies of antiviral regimens for prevention of maternal-fetal transmission

- Evaluations of peer education for the prevention of HIV transmission

Future Actions

NIH will continue to develop new products and initiate new trials of topical microbicides and spermicides to prevent vaginal and rectal transmission of HIV, innovative trials of behavioral and social interventions for sexual and parenteral exposures to HIV, and new studies of interventions to prevent maternal-fetal transmission. The OAR and its Coordinating Committee on Natural History and Epidemiology will continually monitor the NIH research portfolio in these areas.

Recommendation 53 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 3, No. 6]

Identify features of sexual and social networks that determine rates of sexual and perinatal HIV transmission.

Current Status

NIH agrees that it is important to better understand drug use and sexual and other social networks that determine the rates of HIV transmission in vulnerable populations. During the initial stages of the pandemic, ICDs supported studies focused on the examination of single-risk behaviors within vulnerable populations (e.g., gay men and sexual risks; drug-using men and women and multiperson use of syringes). More recently, ICD-supported studies have been examining multiple-risk behaviors across exposure groups and integrating epidemiological models with social science and behavioral science perspectives. This shift in study focus has resulted in more attention to social network research.

NIH recognizes the importance of examining sexual and drug-risk experiences as behavioral transactions between individuals, dyads, triads, and groups. The study of transactional behaviors is critical to the study of HIV because HIV transmission dynamics reflect relational transactions (e.g., sexual intercourse, multiperson use of contaminated syringes). It is especially important to examine mixing patterns within and across networks to help understand this epidemic. NIH recognizes that research on these networks involves exploration of both macro- and micro-level determinants of risk behaviors, including structural, environmental, and demographic factors—particularly, race, class, gender, and ethnicity.

Social network research has been an integral component of NICHD and NIDA research. For example, NIDA is currently supporting studies of HIV transmission risks within networks of drug users, and NICHD is supporting an intervention study involving social networks of STD clinic patients and a study of the dynamics of social sexual networks. These studies use epidemiological

and ethnographic methods applied to study the structure, composition, and dynamics of drug-using networks as they relate to HIV risk behavioral transactions and HIV transmission.

Future Actions

NIH plans to devote more attention to examining behavioral transactions, relational risk behaviors, social-network-based interventions, and risk networks. New PAs or amendments to existing PAs will be issued to encourage more social network research on HIV transmission. For example, NICHD will be issuing a broad PA in FY 1997 to increase support for research on sexual behavior and HIV risk.

Recommendation 54 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 4, No. 7]

> *In close collaboration with scientists studying immunology and pathogenesis, plan and perform interdisciplinary cohort studies of HIV-infected persons with unusual outcomes to elucidate responsible mechanism(s) and identify potentially modifiable risk factors, including opportunistic infections (OIs) and OI prevention, that significantly affect the rate of disease progression.*

Current Status

NIAID has, since 1983, supported multidisciplinary studies comparing persons with differing disease outcomes and/or rates of progression in each of its major longitudinal cohort studies: MACS, WIHS, and WITS. For example, "triplet" studies compare outcome among rapid and normal progressors and long-term nonprogressors. Biological specimens from patients in these three subsets have been distributed to many investigators for additional R01-supported research examining the molecular and cellular basis of disease progression. These include studies focused on the following factors:

- Viral load
- Viral spread and distribution in lymph nodes
- Chemokine receptors
- Major histocompatibility complex distribution
- Viral genotype and phenotype

Other studies, many funded by independent R01s and involving these same cohorts, are examining the effect of OIs on HIV regulation—either directly or by immune activation associated with OIs such as TB.

Unusual outcomes, either specifically related to infection in women or related to late stages of disease progression, also are a special focus of the WIHS. Women-specific issues, such as the relationship between viral shedding and the menstrual cycle, and women-predominant outcomes and OIs, such as pelvic inflammatory disease, are being intensively studied through the WIHS and its collaborators.

In addition, ongoing NIH-supported international studies (in Uganda and South Africa) examine the possible benefits of TB therapy in influencing the rate of HIV disease progression.

Future Actions

NIAID will continue to encourage and facilitate such multidisciplinary research involving collaborations between the cohorts and independent investigators. NIAID is currently distributing a newly completed document entitled "Procedures for Establishing Collaborations to Access Specimens from DAIDS-Sponsored Repositories" that describes procedures for establishing such collaborations. This document also will be available through the Internet on the NIH home page.

Recommendation 55 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 4, No. 8]

> *Recruit high-risk HIV-uninfected cohorts in order to study early diagnosis and treatment of early HIV infection and the influence of particular early immunologic and virologic events on subsequent disease course.*

Current Status

NIAID recognizes acute infection and early therapeutic intervention as one of the most potentially promising areas of scientific research. NIAID currently supports research involving a number of its longitudinal cohorts (WIHS, WITS, HIVNET) studying high-risk HIV-uninfected individuals. NIAID also supports several unsolicited grants (R01s, P01s) and developmental projects (through the CFARs) that focus on early infection, pathogenesis, and treatment.

High-risk infants born to HIV-infected women are recruited into research studies in the PACTG and WITS (cofunded by NICHD) that assess early diagnosis and early aggressive treatment of acute HIV infection as well as immunologic and virologic events related to pediatric disease progression. NIAID supports several R01s from investigators that collaborate with the WITS; these studies focus on intensive evaluation of infected infants and maternal factors that may contribute to infection and the outcomes of early therapeutic intervention in the infants. In addition, NIAID has developed an initiative for FY 1997 to expand studies of perinatal transmission and intervention in the international setting.

Future Actions

For FY 1997 and 1998, NIAID has developed an initiative to create an Acute Infection and Early Disease Research Network. The purpose of this initiative is to support investigator-initiated research using existing cohorts on the pathogenesis of acute infection, immune responses, mechanisms of viral spread during early infection, and the outcomes of early therapeutic interventions. Investigators from all cohorts and clinical trials supported by NIAID have been encouraged to form collaborations and submit applications for the Acute Infection and Early Disease Research Network group initiative.

NIAID will continue to support the cohorts and trials networks that serve as the patient base for all of this research, including support for the early treatment trials within the PACTG and pathogenesis studies of acute infection within the WITS. NIAID will fund the highest quality science that addresses issues of acute infection and early disease, through the initiatives in FY 1997 and 1998 and through other unsolicited applications. NIAID will strive to facilitate greater coordination of these efforts among all involved investigators and with other ICDs.

Recommendation 56 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 4, No. 9]

Develop measures for preventing exposure to opportunistic pathogens and evaluate these measures as they affect the development of OIs in HIV-infected persons. Also evaluate the effect of preventing opportunistic diseases (through preventing exposure to OI pathogens and through primary and secondary prophylaxis) on progression of HIV-mediated immunosuppression.

Please refer to the NIH responses to Recommendations 354–404.

Recommendation 57 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 4, No. 10]

Continue to characterize the full spectrum of illness in certain populations of special interest, including HIV-infected or HIV-exposed infants and children, adolescents infected with HIV, international populations with infections of varying HIV subtypes or clades, and persons in traditional risk groups with unique co-exposures, such as infection with the Kaposi's sarcoma (KS)-associated herpes virus.

Current Status

NIH has provided considerable resources to better understand the natural history of HIV infection, particularly among at-risk populations in a number of cohort studies. Among the ongoing NIH studies that address the areas and populations noted in this recommendation are (1) the WITS—a multi-ICD effort to characterize the spectrum of disease in HIV-infected infants and children infected perinatally; (2) the Hemophilia Growth and Development Study—a multi-ICD initiative to characterize the spectrum of disease in children and young adults infected by contaminated blood products used to treat hemophilia; (3) the Adolescent Medicine HIV/AIDS Research Network—a multi-ICD effort to characterize the spectrum of HIV disease in adolescents infected through injection drug use or sexual intercourse; (4) an NICHD-supported study of maternal virologic factors that may influence the course of disease and transmissibility of HIV infection in Thailand; (5) FIC's AITRP-supported studies of HIV-1 and HIV-2 in Senegal and studies of varying HIV subtypes in Thailand and India; and (6) a subproject within the multi-ICD WIHS that is investigating clinical disease progression and virologic and immunologic parameters in women coexposed through sexual and parenteral routes to HIV and other infectious diseases.

The OAR Coordinating Committee on Natural History and Epidemiology reviews and updates the NIH Plan for HIV-Related Research, which, following external peer review, provides general guidance to ICDs in the planning and support of research programs to address identified research needs, such as those expressed in this recommendation.

Among the most important questions are whether varying HIV subtypes or clades are transmitted more efficiently by type of exposure (e.g., sexual, parenteral) and whether these subtypes differ in pathogenicity. International studies are particularly critical to monitoring the spectrum of HIV subtypes in other countries that potentially could become established in the United States. Variations in HIV subtypes also have implications for HIV vaccine development and may pose problems with detection of HIV using current commercial test kits. Another question generated by NIH research is whether various OIs may act to exacerbate the HIV disease process by increasing viral load, as may happen with TB and bacterial pneumonia. As HIV-infected persons receive improved therapies and live longer, there is a need to monitor whether long-term survivors may present with new disease manifestations. Further, NIH longitudinal studies of women and children have highlighted the need to follow apparently uninfected children born to HIV-infected mothers to ensure that latent chronic infections with long-term consequences have not occurred and also to evaluate any possible long-term sequelae from having been exposed to antiviral drugs *in utero*, at birth, or shortly after delivery. NIH studies also have highlighted a need for more attention to be given to the roles that *in utero* illicit drug exposure, adolescent substance abuse, and nutritional deficiencies may play in the transmissibility, susceptibility, and natural history of HIV disease.

Future Actions

The OAR Coordinating Committee on Natural History and Epidemiology will review this recommendation in view of the FY 1998 NIH Plan for HIV-Related Research and any recently initiated studies or special initiatives that may already have been performed by the ICDs in this area. The Coordinating Committee will recommend that certain ICDs consider launching new initiatives to address any gaps it identifies through this review.

II. SUBPANEL REPORTS

A. Sexual Transmission Subpanel Report

Recommendation 58 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 15, No. 1]

Define how mucosal HIV shedding and transmission are influenced by viral subtype, local immune responses, cervical ectopy (in adolescent and young women), HIV infection stage, antiretroviral treatment, and experimental vaccines. Identify factors such as genetic and immunologic parameters associated with host susceptibility or resistance.

Please refer to the NIH response to Recommendation 51.

Recommendation 59 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 15, No. 2]

Continue and broaden ongoing intervention trials on such factors as topical microbicides and early diagnosis and treatment of STDs, and consider appropriate designs for innovative prevention research on such potentially important factors as cervical ectopy, circumcision, and hormonal contraception.

Please refer to the NIH response to Recommendation 52.

Recommendation 60 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 15, No. 3]

Identify the social and ecologic determinants, including sexual and social networks, that account for variations in the distribution of infection and disease, including the role of demographic factors such as socioeconomic status, race, ethnicity, and age.

Please refer to the NIH response to Recommendation 53.

Recommendation 61 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 15, No. 4]

Develop rapid, inexpensive, and simpler diagnostic tests for STDs to facilitate treatment, thereby strengthening prevention and control of HIV and STDs.

Current Status

Development of STD diagnostic tests is an extremely high priority for the NIAID, and over the past several years, NIAID has supported multiple activities towards this goal. In 1991, NIAID and the USAID sponsored a collaborative meeting on the development of rapid and inexpensive STD diagnostic tests. This collaboration resulted in the establishment of the STD Diagnostics

Initiative, an international task force to facilitate the development of the tests. In 1994, a small grants program cofunded and coadministered by NIAID was begun as a part of this initiative. In 1993, NIAID solicited SBIR grants and contracts for STD diagnostic research. As a result of research funded through the SBIR initiative, a medical diagnostic manufacturer has submitted yeast and vaginitis tests for approval to the FDA, and another medical diagnostic manufacturer has developed a hybrid capture assay for genital herpes.

NIAID also collaborated with the Rockefeller Foundation to identify criteria for the Rockefeller Prize ($1 million, Rockefeller monies) for an STD diagnostic test for gonorrhea or chlamydial infection. NIAID is funding four Cooperative Agreements for the development and manufacture of rapid, inexpensive STD diagnostic tests for gonorrhea and chlamydial infection totaling $10 million over 4 years. In addition, numerous clinical trials are in progress which, in part, are designed to evaluate some of the newly developed tests of this genre.

Future Actions

NIAID will continue to support these successful programs and will expand research in this area pending funding availability.

B. Perinatal/Postnatal Transmission Subpanel Report

Recommendation 62 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 17, No. 1]

Develop modalities to minimize perinatal transmission that extend benefits of chemoprophylaxis, including hyperimmune globulin and combination chemotherapies.

Current Status

NIH is working to build on the success of ACTG 076, the trial that demonstrated the efficacy of AZT in reducing perinatal transmission of HIV. In this effort, a high priority has been given to developing combination chemotherapies. NICHD, NIAID, and NHLBI are collaboratively funding, through the PACTG, an ongoing trial (ACTG 185) to assess the efficacy of HIVIG, infused monthly in infected pregnant women starting at 20 weeks gestation and once to the neonate at birth, in combination with AZT for prevention of perinatal transmission in a relatively ill maternal population (CD4+<500). This trial, which is being conducted in concert with ACTG 076, has enrolled more than half of the planned 800 patients. Several important pathogenesis-based questions are also being evaluated in the context of this new trial, including evaluation of the maternal virologic and immunologic factors associated with transmission risk and the utility of new innovative methods for early diagnosis of infection in the infant.

The collaborative NIAID/NICHD PACTG has developed a perinatal transmission trial (ACTG 316) to evaluate the efficacy of a simple regimen of oral neviripine given once to infected women during labor and once to the neonates at 48 hours old in combination with AZT for reducing vertical transmission. This trial also is being conducted in concert with the ongoing ACTG 076 trial.

The PACTG also is evaluating a number of other antiretrovirals, including didanosine (ddI) and stavudine (d4T), in pregnant women in combination with AZT in Phase I/II studies. Additional agents that are planned to be evaluated in combination trials during the next 6 to 9 months include ritonavir, indinavir, nelfinavir, and 1592U89. The safety and pharmacokinetics of these drugs also will be evaluated in HIV-exposed neonates. The safety and immunogenicity of envelope-based recombinant HIV vaccines have been evaluated in HIV-infected pregnant women (ACTG 235) and are under evaluation in HIV-exposed neonates (ACTG 230), and a newer live recombinant avipox HIV vaccine will be evaluated in neonates in the near future (ACTG 326). Additionally, Phase I studies of monoclonal antibodies are planned to be tested in infants born to infected mothers. These studies are being conducted to provide a basis for future active and/or active/passive perinatal infection prophylaxis trials.

Simpler modalities also are being evaluated in international trials that are funded through a variety of mechanisms (HIVNET, R01s). These modalities include HIVIG given once to pregnant women in late gestation and once to neonates at birth; HIVIG given only to the neonate; neviripine in labor and to the neonate as sole therapy; shorter modifications of the ACTG 076 AZT regimen; vitamin A supplementation; and breast- versus bottle-feeding.

The ongoing perinatal clinical trials being conducted by NIH are integrated with and complementary to perinatal trials being conducted by other national and international agencies. NIH is represented on the Working Group on Perinatal Transmission of the UNAIDS. The Working Group consists of representatives from NIH, CDC, the World Health Organization (WHO), and other major international groups conducting perinatal trials (European Collaborative, Agence Nationale de Recherches sur le Sida of France, etc.). This Working Group has met two to three times yearly since the results of ACTG 076 were announced to discuss ongoing and planned trials to avoid duplication of efforts on a global basis.

Future Actions

During the coming year, NIH will have two major ongoing Phase III perinatal trials (ACTG 185 and 316) to evaluate immune-based and combination therapy to reduce perinatal HIV transmission. In addition, several Phase I/II trials of combination antiretroviral therapies and immune-based therapies (HIV vaccines/monoclonal antibodies) are currently or will soon be under evaluation within the PACTG, and a number of international trials are evaluating simpler prevention modalities.

Recommendation 63 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 17, No. 2]

> *Evaluate low-cost prevention strategies for resource-poor settings, such as intrapartum antisepsis, short-course antiretroviral prophylaxis, vitamin supplementation, and shortened duration of breast-feeding.*

Current Status

NIH currently supports a number of studies on low-cost interventions designed to prevent or reduce the transmission of HIV from mother to fetus/child through such funding mechanisms as NIAID's HIVNET program, individual R01 grants, and the FIC AITRP. These NIH-funded international studies include (1) a study of the impact of breast milk versus formula feeding in Kenya; (2) several studies of the role of vitamin A and micronutrients in the reduction of vertical transmission of HIV in Uganda and Tanzania; (3) a study of modified ACTG 076 regimens in reducing the transmission of HIV from mother to fetus/child in Thailand; (4) an evaluation of maternal virologic and immunologic factors that may affect transmission risk from mother to fetus/child in Thailand as a prelude to the development of vaccines for childbearing and pregnant women; and (5) an evaluation of microbicides to reduce sexual transmission in Kenya (under HIVNET) and in Cameroon (through the R01 grant mechanism).

Low-cost prevention strategies have been emphasized in the Natural History and Epidemiology and Vaccines sections of the NIH Plan for HIV-Related Research. In addition, these strategies are addressed in the recently completed *ad hoc* review of the HIVNET recommended by the NIH AIDS Research Program Evaluation Task Force. The HIVNET review panel made a number of useful recommendations to further enhance what it considered to be an exceptionally well-managed and coordinated effort. Among the issues that may need further discussion is a better understanding of which Federal agencies should be responsible for operations research once additional efficacious interventions are identified.

It is essential to remember that developing countries range from having very minimal to no resources for health care, to moderate and growing resources in some settings (e.g., Kenya, Thailand). Thus, the term "low cost" is a relative one and must be considered in context. Efforts will continue to coordinate NIH activities in this area with those of UNAIDS.

Future Actions

NIH will continue to encourage the submission of investigator-initiated R01 research grants in this area; emphasize this area within AITRP; work to ensure that adequate research capacity exists at foreign sites to conduct important prevention research studies of potential benefit to the United States and foreign collaborators; develop brief behavioral interventions that could be tailored to different cultural groups and used with illiterate populations; and continue to work with nongovernmental partners to gather additional attention, support, and input to this vital area. A workshop currently under development by FIC to address prevention research also may help to encourage new efforts in this area and perhaps help in the development of a trans-NIH PA, if appropriate.

Recommendation 64 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 17, No. 3]

Design and test behavioral and social intervention strategies specifically for HIV-infected, pregnant women regarding therapies to reduce vertical HIV transmission.

Current Status

NICHD has been continually involved in this issue since 1987, supporting multiple R01 grants on reproductive decision-making in women with and at high risk for HIV infection. After the successful completion of ACTG 076, NIAID and NICHD participated with the Agency for Health Care Policy and Research (AHCPR) in developing materials to educate and inform pregnant women about decision-making. The NICHD also chaired a national task force charged with developing recommendations on counseling and testing of pregnant women in the post-076 era. Finally, NIAID and NICHD have worked with the Health Resources and Services Administration (HRSA) to evaluate its initiatives that are implementing AZT programs for pregnant HIV-infected women at multiple sites. NIAID and NICHD continue to be available to HRSA for consultation.

Preliminary epidemiological studies have begun to identify a constellation of risk factors that may be associated with perinatal transmission, some of which are amenable to interventions (e.g., inadequate nutrition, failure to maintain general health, substance abuse, and smoking). Ensuring that pregnant women seek prenatal care is therefore an important prevention strategy that involves initiating and maintaining medical care. However, more basic research is needed on women's attitudes, values, and beliefs about vertical transmission and on the broader issue of reproductive decision-making to underpin the design of interventions for pregnant women who want to assess whether AZT or other medical treatments should be initiated during pregnancy.

It is essential to recognize the particular complexity of reproductive decision-making for women who have substance abuse problems. In this regard, NIDA is supporting research within the NIAID/NICHD-sponsored WITS to examine a three-phase process in pregnant women's consideration of antiretroviral treatment for HIV infection: (1) acceptance in principle, (2) initiation of treatment, and (3) adherence to therapy. The data resulting from this study may provide important information for the design of behavioral and social interventions for HIV-infected pregnant women who are dealing with substance abuse.

Future Actions

NICHD will continue to support investigator-initiated activities in the areas of effectively drawing pregnant women into prenatal care and decision-making around sexual partner choice and reproductive issues. Several PAs will be developed to expand NICHD's substantial investigator-initiated research activities in these and related areas. NICHD also will be supporting studies to understand sexual risk behavior of HIV-infected individuals. NIMH is planning a preliminary advisory meeting and developing a concept paper on behavioral issues in vertical transmission. Other ICDs will participate in the meeting and possibly cosponsor a PA in this area.

NIDA is actively seeking additional research through a PA, entitled "HIV-Related Therapeutics in Drug Users," on strategies to enhance recruitment and retention of drug users in protocols for HIV-related therapeutics, including protocols to address vertical transmission.

Recommendation 65 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 17, No. 4]

Determine the long-term effects of in utero *exposure to HIV and antiretroviral prophylaxis, including the emergence of drug resistance in both HIV-infected mothers and infants.*

Please refer to the NIH response to Recommendation 27.

C. Parenteral/Injection Drug Use Transmission Subpanel Report

Recommendation 66 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 18, No. 1]

Conduct prevention studies, including RCTs, to assess how increasing access to sterile syringes via syringe-exchange programs, retail pharmacy sales, and other methods affects HIV transmission and drug use behaviors.

Current Status

NIDA initiated a program of research targeting needle/syringe exchange in 1994 and has funded 15 grants focused on examining the effectiveness of needle/syringe exchange programs (NEPs) on reducing HIV behavioral risks (e.g., research on multiperson use of contaminated syringes) and preventing the transmission of blood-borne viruses such as HIV and hepatitis. A considerable range of investigator-initiated research is manifested in the study designs, data collection methods and measures (biological endpoints, behavioral risk/outcomes), sampling targets/accruals, and analytic plans.

NIDA supports RCTs and has recently funded a grant that will use a randomized design to examine the relative efficacy of pharmacy sales versus NEPs on reducing risk behaviors and the transmission of hepatitis B and C and HIV. All participants in the study receive education about HIV prevention and risk reduction as well as education about the existence of the hepatitis B vaccine, and all are offered HIV testing and counseling, including transmission prevention counseling in the case of a positive test result.

Notwithstanding the merits of RCTs, they are not always feasible or appropriate to deploy. A host of factors can undermine the feasibility and even utility of RCTs. For example, a project may not be replicable and the cost of an RCT not justifiable; the potential for intergroup contamination may not be possible to control; there may not be community support for RCTs; it may not be possible to match and randomize communities if they are the desired unit to receive an intervention and analysis; there may be ethical problems in withholding experimental treatments; or policy changes that affect HIV risk taking (such as the availability of treatment or syringe exchanges) may occur too swiftly for an experiment to be mounted. Investigators are encouraged to carefully review and consider such drawbacks to RCTs as well as weigh the strengths of various quasi-experimental designs that may present reasonable and often less costly alternatives to RCTs.

Researchers in NIDA-funded NEP studies have relied on nested case control designs, retrospective and prospective cohort designs, the use of existing cohorts from different geographical areas (high, medium, and low HIV seroprevalence), and the use of epidemiological and ethnographic approaches, in combination with biological measures, to determine the effectiveness of NEPs on HIV risk behaviors and a range of biological outcomes. NIDA has focused the impact of NEP service components on HIV risk behaviors among injection drug users (IDUs).

Future Actions

NIDA will, through ongoing and new PAs, encourage (1) the use of randomized community trials where appropriate and (2) the creation of multisite databases, which will permit analyses of pooled data and the support of studies on the operations and impact of NEPs on risk behaviors, access and utilization of prevention and health services, and seroincidence.

Recommendation 67 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 19, No. 2]

> *Evaluate the social, cultural, and economic factors, including social networks, that influence specific drug-using practices (including injection of various drugs) and the prevalence and incidence of HIV infection among drug users.*

Current Status

NIDA agrees with the Panel's recommendation and plans to continue to support research in these areas, particularly research addressing questions concerning how changes in the structure and composition of networks affect risk behaviors, how the dynamics of HIV transmission are related to these changes, and how to use networks to prevent the spread of HIV infection. NIDA's research portfolio has included study of the context of HIV risk behaviors as one of the myriad factors that influence and determine whether an individual will engage in such behaviors. Understanding contextual issues for injecting and noninjecting drug users, sex partners of drug users, and special populations (such as women, minorities, and gay or bisexual men) remains an important challenge to the AIDS research community. Currently, NIDA is supporting 19 studies on behavioral risk factors; the determinants of these risk factors; and the incidence and prevalence of HIV infection in multiracial, multiethnic, male and female populations in low, medium, and high seroprevalence areas across the United States. In addition, NIDA supports 10 investigator-initiated projects related to social networks, drug use, and HIV transmission.

Data provided from other ICD-supported population-based studies on the determinants of the formation of social networks of drug-using individuals, for example, the NICHD National Longitudinal Study of Adolescent Health (Add-HEALTH), also are providing useful information in this regard.

Future Actions

NIDA intends to support research proposals submitted in response to a newly released PA that focuses on drug use, sexual risk behaviors, and HIV infection in drug-using men who have sex with men (DU MSM). NIDA is redirecting some of the epidemiology and network paradigm research to focus on both sexual networks of drug users and the drug-using networks of those at risk for HIV. Because DU MSM may engage in both high-risk drug use and sexual practices and may have multiple and different drug use and sex partners and networks, they not only constitute an important HIV risk group in and of themselves but also have the potential to serve as a bridge for HIV transmission to heterosexual IDUs and non-DU MSM. Promising directions for the epidemiology and prevention of HIV in this dual risk group will draw from cumulative research related to the epidemiology and prevention of HIV infection in MSM, IDUs, and non-IDUs.

Recommendation 68 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 19, No. 3]

Investigate interactions of IDU and IDU-related behaviors on viral load, viral subtype, and viral shedding.

Current Status

NIDA participates in the HIV Epidemiology Research Study (HERS), a multiagency collaborative study that will define the trajectories of molecular (HIV-1 RNA copies) and infectious HIV load among women who are drug users, in order to determine the *in vivo* effect of cocaine and opiates on viral burden, to determine the critical viral load among rapid and long-term progressors, and to perform molecular studies of genetic variation and recombination and biological/functional studies (cell tropisms, phenotypic variation, neutralization).

In early 1995, NIDA issued a PA entitled "HIV Disease Progression in Drug Users." This PA emphasizes the need for research that links behavioral, immunologic, genetic, and virologic factors in disease progression/pathogenesis studies.

Areas of research interest include viral and host factors important in infection and subsequent disease course. This PA also focuses on the consequences of repeated inoculation of virus through injection and/or sexual exposure on clinical course; immune parameters; viral phenotype, genotype, and load; and the evolution of virus heterogeneity.

NIDA is supporting research, through investigator-initiated grants and NIH-supported multisite studies, on the pathogenic correlates of disease progression in epidemiologically well-characterized cohorts of active and former injectors, both in and out of drug abuse treatment.

Currently funded research includes integrated studies of the effects of drug use (frequency, injection versus noninjection, drug type) and route of infection (injection and/or sexual exposure) on virologic and immunologic factors, such as viral load, nucleotide sequence, viral phenotype, humoral and cellular response, as well as correlates of protective immunity (chemokines, CD8 suppression) in high-risk seronegatives.

Future Actions

NIDA will continue supporting research on the correlates of HIV disease progression in current and former IDUs and will continue multiagency collaborations in this area as appropriate. For example, a multiagency collaboration (WIHS) will examine the course of disease in women (as measured by clinical disease progression, viral load, nucleotide sequence, viral phenotype, and humoral and cellular responses) infected mucosally and those with parenteral and mucosal exposure and will examine the consequences of repeated antigenic stimulation and immune activation (drug use, STDs). In addition, a recently funded supplement to the WIHS will enable its PIs to assess HIV virology and immunology in the genital tract of drug-using women by examining cervicovaginal lavage specimens in dual-risk IDUs, drug users who do not inject, and drug-free individuals. The potential use of international cohorts in Southeast Asia might help to understand the interactions between injection drug use and viral subtype.

Recommendation 69 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 19, No. 4]

> *Conduct research necessary for the development of new methods for the decontamination of syringes and other drug use equipment, including research on the survival and transmissibility of HIV on IDU paraphernalia.*

Current Status

NIDA has conducted research on the efficacy of various decontamination strategies for needle/syringes containing HIV-contaminated blood. This research led to the observation that household bleach could be useful in reducing the risk of HIV transmission if adequate contact time was achieved. However, observations of drug users attempting to decontaminate paraphernalia are consistent with the conclusion that IDUs are unlikely to be able to consistently perform these tasks in a reasonably effective manner.

NIDA continues to support and encourage research on methods for syringe decontamination through an ongoing PA entitled, “Research on Needle Hygiene and Needle Exchange Programs.” To date, the majority of research projects submitted in response to this PA have evolved from studies of decontamination procedures to studies of methods to increase the availability of sterile injection equipment and to better describe and characterize drug injection behaviors related to risk of HIV transmission.

Future Actions

More recent studies have identified HIV DNA in injection paraphernalia other than needles and syringes. NIDA agrees with the recommendation and will continue to conduct research on the extent and types of injection-related risk behaviors, the survival and transmissibility of HIV related to these behaviors, and practices to reduce transmission risk by reducing or eliminating HIV through various decontamination procedures. NIDA also will conduct research on the degree to which addicts are able to learn to avoid drug paraphernalia including contaminated cookers, cottons, and wash waters.

D. Natural History/Disease Progression Subpanel Report

Recommendation 70 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 21, No. 1]

Perform interdisciplinary studies of HIV-infected persons with unusual outcomes, including rapid progressors, nonprogressors, and persons with persistently low CD4 counts in the absence of clinical disease.

Current Status

Since setting a priority for this research in 1983, NIAID has supported multidisciplinary studies comparing persons with differing disease outcomes and/or rates of progression in each of the major cohort studies, including MACS, WIHS, and WITS. Biological specimens from patients in various progression categories have been distributed to many investigators for additional R01-supported research examining the molecular and cellular basis of disease progression. Unusual outcomes, particularly those related to late stages of disease progression, also are a special focus of the WIHS.

In addition, please refer to the NIH response to Recommendation 54.

Recommendation 71 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 21, No. 2]

Identify factors that significantly affect the rate of disease progression and amount of viral shedding that could be useful to the development of new interventions.

Please refer to the NIH response to Recommendation 51.

Recommendation 72 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 21, No. 3]

Recruit high-risk HIV-uninfected cohorts in order to study early diagnosis and treatment of infection, the effects of particular immunologic and virologic characteristics at the time of infection on long-term disease course, and the correlates of protection among multiexposed persistently uninfected persons.

Current Status

NIH agrees with the Panel that the recruitment of high-risk HIV-uninfected cohorts to study early diagnosis and treatment of infection is an area of high priority. A number of research activities addressing this issue have been implemented or are being planned. These include the following:

- An initiative to develop an Acute Infection and Early Disease Research Network
- Studies involving high-risk infants born to HIV-infected women

- An initiative to expand studies of perinatal transmission and intervention in the international setting

- Research in longitudinal cohorts (WIHS, WITS, HIVNET) that include high-risk HIV-uninfected individuals

- Several unsolicited grants (R01s, P01s) and developmental projects (through the CFARs), many of which involve collaborations with established cohort studies

In addition, please refer to the NIH response to Recommendation 55.

Recommendation 73 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 21, No. 4]

Identify biological and sociobehavioral risk factors for OI and evaluate the potential of targeting these risk factors in preventive interventions.

Current Status

NIH recognizes the importance of better identifying both biological and sociobehavioral risk factors that contribute to OIs and that could be targeted with preventive interventions. Currently, National Institute of Nursing Research (NINR) is supporting a study to prevent oral candidiasis among HIV-infected persons that involves a well-developed educational intervention designed to promote diet modifications to reduce the amount and length of time sugars are in the mouth, improve oral hygiene, and increase recognition of signs and symptoms of oral candidiasis. NINR also supports a study testing a pharmacological prevention protocol for vaginal candidiasis, and NIAID funds several grants that support research on exposure and biological risk factors associated with OIs.

Future Actions

The OAR Coordinating Committee on Natural History and Epidemiology will consider this topic during the development of the FY 1999 NIH Plan for HIV-Related Research.

Recommendation 74 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 21, No. 5]

Continue to characterize the full spectrum of illness on certain populations of special interest, including HIV-exposed or HIV-infected infants, children, and adolescents; international populations with infections of varying HIV subtypes or clades; and persons from all risk groups with unique co-exposures, such as infection with the KS-associated herpes virus.

Please refer to the NIH response to Recommendation 57.

E. Methodology Subpanel Report

Recommendation 75 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 23, No. 1]

Use methodologic guidelines for HIV prevention trials research analogous to the trial-phasing system in pharmaceutical research, ensuring an orderly sequence of prevention studies, from the identification of potentially modifiable risk factors for HIV transmission to the identification and evaluation of interventions to interrupt transmission and the systematic application of research results in well-defined populations.

Recommendation 76 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 23, No. 2]

Require and support the rigorous study designs essential in HIV prevention research. This may require levels of funding comparable to those used in clinical trials of pharmaceuticals, and the NIH should provide the levels of support necessary to conduct such research.

Current Status

NIH acknowledges the importance of devoting resources to methodological research; this priority is articulated in the FY 1998 NIH Plan for HIV-Related Research. Further, NIH agrees that the most rigorous study designs should be used and that a phased-in trials approach analogous to the pharmaceutical research paradigm has considerable potential for improving the science of prevention. Some ICDs are supporting community-randomized designs for HIV prevention trials and have employed the trial phasing scheme to characterize their research portfolio. For example, NIDA's behavioral therapies program supports Phase I research to develop/pilot test theory-based therapies, Phase II efficacy trials, and Phase III research on transferring efficacious therapies to community programs. NIMH convened 30 behavioral scientists who prepared a four-phase system that is being used by the NIMH Office on AIDS to describe its research portfolio.

However, RCTs may not be the only schema for planning and evaluating HIV prevention science. There are a host of special methodological issues in community field trials with populations that are hard to reach and difficult to access, recruit, engage, intervene with, and follow over time. Indeed, the tension between the idealized method of RCT and the reality of conducting and testing interventions in certain populations and settings was evident in the inconsistent recommendations in the Natural History, Epidemiology, and Prevention Research Area Review Panel report and the Behavioral, Social Science, and Prevention Research Area Review Panel report, where the former contended that the randomized trial design should always be the standard for prevention science, while the latter acknowledged that a broader range of methods was appropriate for addressing different questions in prevention science. NIH concurs that the RCT should be employed when possible and appropriate. However, the characteristics of vulnerable populations and the issues related to drug use and sexual behavior (e.g, often illegal, hidden, and stigmatized) within them require careful attention to community participation and ethical concerns related both to research design and study recruitment. Moreover, in selecting interventions in the HIV epidemic, there is frequently a conflict between internal and external validity and choices often are made that involve balancing between degree of rigor and degree of

applicability. The controlled experiment may provide the greatest rigor and may provide the best strategy for direct tests of narrow hypotheses regarding vaccines, treatments, and individual behavior change. However, at the community level, the RCT may be used only on special conditions but not for complex community interventions of long duration that are aimed at changing social norms (e.g., values, expected behavior, and actual behavior). Clearly, effective research designs must be matched to clearly defined questions, and this may necessitate less rigor in order to test relevant AIDS prevention programs.

Future Actions

OAR will take the lead in planning a 1997 meeting to review and discuss the advantages and disadvantages of applying the clinical trial phasing model to HIV prevention studies. This meeting would involve NIH scientific program staff, nongovernmental researchers, and community representatives.

In addition, please refer to the NIH response to Recommendation 77.

Recommendation 77 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 23, No. 3]

Support a comprehensive program of interdisciplinary methodologic research on the statistical design and analysis of community randomized HIV-prevention trials and on field studies and theoretical models of the role of social networks in HIV transmission.

Current Status

NIH agrees with the recommendation to support a program of interdisciplinary methodological research involving community-randomized trials. NIH also agrees that methodologies to study the structure of social networks should be developed by a multidisciplinary team of theoretical and applied statisticians/modelers, epidemiologists, sociologists, and anthropologists. Some ICDs with multisite trials devote attention to methodological issues as part of their program, and some ICDs have contracts and RFAs to solicit and support methodological studies.

RCTs

As discussed in the response to **Recommendations 75 and 76,** there are special methodological challenges inherent in the design of RCTs at the community level. These challenges include the need to develop subsampling designs to understand the mechanics of HIV interventions and dissemination of effects throughout a community; improve methods for monitoring community subpopulations involved in HIV transmission; and develop methods of statistical analysis at the community level.

Networks

NIH agrees that more research must be undertaken on the context of HIV risk among drug users, social/risk networks of drug users, and sexual-risk networks. Within the social network

framework, a number of methodologies have received attention, including epidemiological modeling of transmission dynamics, ethnographic mapping and observation, and methodologies sampling schemes appropriate to the specific study populations. In addition, please see the NIH response to **Recommendation 53.**

While much of the network research to date has focused on drug-using networks, more research on sexual and other social networks is necessary. Improved methodologies of network analysis will increase understanding of the changes in the structure and composition of these networks, the changes in risk behaviors, the dynamics of HIV transmission related to these changes, and the use of these networks for preventing the spread of HIV infection.

Future Actions

Methodological research is identified as a research priority for behavioral and social science research in the FY 1998 NIH Plan for HIV-Related Research. The Coordinating Committee on Behavioral, Social Science, and Prevention Research will consider the merits of holding a meeting to review the methodological issues involved in mounting RCTs as well as to review progress with respect to developing network analysis. Particular attention will be given to new methodological strategies to sample, recruit, engage, intervene with, and follow hard-to-reach, often hidden populations whose risk behaviors expose them to the potential for HIV transmission.

In addition, please refer to the NIH response to Recommendation 75 and 76.

Recommendation 78 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 24, No. 4]

Develop guidelines for systematic structured reporting of HIV prevention research studies that are analogous to those now required by many journals for reports of clinical trials, and establish and sponsor a collaborative prevention trials review and evaluation group (a Cochrane Collaborative Group) to maintain the database and continually monitor and assess the state of HIV prevention research.

Current Status

NIH concurs with the Panel on the need to develop an NIH-wide systematic reporting system to record the protocols and findings of HIV prevention research. However, at present each ICD has a system for reporting its specific prevention research portfolio and has produced compendia of general findings from its sponsored projects for different purposes and audiences (e.g., Congress, advisory committees, Federal agencies, professional journals). Linking these ICD compendia to a larger and more systematic database, such as those constructed by Cochrane Collaboration Groups, may be one approach to consolidating information from prevention science research.

Cochrane Collaboration Groups are relatively *ad hoc* groups of people with a common interest in a particular health care topic who agree to establish and maintain a database of systematic reviews of RCTs in that topical area. Cochrane Centers, located throughout the world, consolidate these

reviews into a larger database. The Cochrane effort resulted from the belief that systematic reviews of evidence from RCTs would contribute to the rational use of health care resources.

Future Actions

The OAR Coordinating Committees in Behavioral and Social Science and Natural History and Epidemiology, as well as the OARAC PSWG, will review this recommendation for the FY 1999 NIH Plan for HIV-Related Research. The potential of a Cochrane Collaborative Group will be explored in conversations with the CDC, which has recently funded a contract for a "Cumulative Research Synthesis System for HIV/AIDS Behavioral and Social Science Intervention Studies" [RFP 200-96-0520(P)].

III-IV. REVIEW OF NATURAL HISTORY, EPIDEMIOLOGY, AND BIOMEDICAL PREVENTION RESEARCH AT THE NIH BY SCIENTIFIC PRIORITIES AND BY INSTITUTES AND CENTERS

A. National Institute of Allergy and Infectious Diseases (NIAID)

Recommendation 79 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 28, Nos. 1–4]

Recommendation 79, Part 1

Redirect NHEBP funding within the clinical trials networks to evaluate the effects of antiretroviral therapy on mucosal shedding of HIV.

Current Status

NIAID has recently initiated several pilot studies to examine the relationship between plasma viral load and mucosal shedding of virus. These studies were originally sponsored through the DAIDS Treatment Research Initiative (DATRI) and are now being carried on by the WIHS, ACTG, and WITS in collaboration with NICHD. Examples of the studies initiated include the following:

- A pilot study to assess the influence of menstrual cycle stage on the expression of HIV-1 in vaginocervical secretions from HIV-seropositive women. This is a prospective study of 15 women and includes frequent and intensive clinical visits for weekly collection of vaginocervical secretions and blood for immunologic and virologic evaluations.

- A pilot cross-sectional study of women at various stages of the menstrual cycle to evaluate HIV shedding as well as immune responses (including neutralizing antibodies and cellular immune responses) compared with plasma levels of virus.

- An assessment of the relationship between herpes simplex virus type 2 (HSV-2) shedding in vaginocervical secretions and HIV-1 plasma viral load in HIV-infected individuals. This study will examine the influence of HSV-2, which results in HIV activation.

For these projects, women are being enrolled from the WIHS, and laboratory studies are being supported by the WIHS, ACTG, and other grant-supported laboratories. NICHD is also supporting collection and analysis of the data from these studies.

Future Actions

The pilot studies described above will set the groundwork for further studies evaluating the effect of antiviral treatment on viral shedding. NIAID will work with advisors and investigators to assess the status of this scientific area and facilitate additional work as needed.

Recommendation 79, Part 2

Review studies of seropositive or seronegative cohorts periodically by a multidisciplinary panel of experts to ensure that all opportunities for productive and high-priority research are adequately addressed. Such reviews should be coordinated by the OAR to facilitate inter-Institute cooperation.

Current Status

Since 1991, NIAID has conducted such reviews of major programs, including cohort studies, as an important means of shaping the programs' future in their periodic recompetition. The MACS, WITS, and WIHS have all been reviewed by nongovernmental panels under the auspices of ARAC. Other ICDs that cosponsor these programs and the OAR also have participated. Most recently, NIAID and OAR cosponsored an external review of the HIVNET (in response to the NIH AIDS Research Program Evaluation Task Force). Reports and recommendations are presented to the ARAC and are implemented by ICD program staff in developing new and/or renewal initiatives. The investigators themselves also implement recommended changes when appropriate to improve the program. The results of the HIVNET review also were presented to the OARAC in October 1996.

The following programs and program areas were subjected to systematic review by NIAID:

1992 Centers for AIDS Research (CFAR)
Community Program for Clinical Research on AIDS (CPCRA)
National Cooperative Vaccine Development Group (NCVDG)

1993 Pathogenesis Research
AIDS Clinical Trials Group (ACTG)
Pediatric HIV Research—including WITS

1994 Epidemiology Research—including MACS
AIDS Vaccine Evaluation Group (AVEG)

1995 Preclinical HIV Vaccine Research
Planning Workshop for National Community Advisory Boards Review

1996 Women's Interagency HIV Study (WIHS)
HIV Vaccine Efficacy Trials Network (HIVNET)

Future Actions

NIAID will continue to convene program review panels of multidisciplinary experts to assist in focusing and improving its research programs. The OAR and relevant ICDs will participate as appropriate.

Recommendation 79, Part 3

Augment the epidemiologic expertise of cohort study investigators by recruiting investigators with expertise in basic, clinical, social, and behavioral sciences. The need for multidisciplinary research teams extends to investigators using repository specimens.

Current Status

NIAID concurs with the Panel recommendation and has a long record of encouraging multi-disciplinary research in each of its major cohort studies: MACS, WIHS, WITS, and HIVNET. For example, within the MACS, separate pathogenesis laboratories have been established to enhance the expertise associated with the primary protocol and to ensure peer review of the science. Similar approaches to broaden the base of investigator-initiated research will be developed by the investigators of the WITS and WIHS as they are recompeted.

In addition, each group collaborates with outside investigators on independently funded investigator-initiated research and makes samples available from the cohort studies to other researchers.

NIAID has just completed preparing and is now distributing a document to help scientists form collaborations with the epidemiologic and clinical cohorts that it supports. Strengthening the linkage between the cohorts and non-study-investigators to maximize the quality of the scientific questions being addressed is critical to the Institute.

Future Actions

NIAID will continue to foster, encourage, and facilitate collaborations between basic, clinical, epidemiological, social, and behavioral science investigators to maximize basic research and the scientific productivity of these groups, particularly in the areas of pathogenesis and transmission research.

Recommendation 79, Part 4

The NIAID Centers for AIDS Research Program should include the investigation of epidemiology, natural history, and prevention as a specific aim, with the goal of increasing benefit to public health.

Current Status

NIAID supports the CFAR program to promote collaborations between clinical and basic scientists with the ultimate goal of expediting research and improving public health. The ARAC, in its approval of revisions to the CFAR program, stipulated that each CFAR should include one basic, one clinical, and one developmental core. The specific cores should be based upon the

strengths and needs of each institution. In this context, core activities related to epidemiology, natural history, and prevention will be encouraged, but NIAID will not mandate that specific cores be included.

Future Actions

NIAID will continue to encourage CFARs to support a full spectrum of AIDS research activities, including epidemiology, natural history, and prevention-related research, as best fits the specific needs and scientific expertise of each institution.

In addition, please refer to the NIH response to Recommendation 40.

B. National Heart, Lung, and Blood Institute (NHLBI)

Recommendation 80 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 29, Nos. 1–3]

Recommendation 80, Part 1

Transfer funds currently supporting developmental investigations of artificial blood substitutes and research on the safety of the blood supply to other high-priority areas in biomedical prevention and epidemiology.

Current Status

NHLBI is not permitted to transfer funds from programs where the commitment has already been made. The NHLBI does plan to cut the resources supporting new programs in blood safety and has re-appropriated this money to other areas that are of higher priority. Besides a request for continued funding for a surveillance study of blood safety, NHLBI has no new plans for any blood safety program efforts. Resources have been allocated to programs such as the study of the role of passive immunotherapy and gene therapy in prevention and treatment of HIV infection and studies of TB.

Recommendation 80, Part 2

Review ongoing pathogenesis studies of cardiopulmonary and hematologic complications of HIV infection for opportunities to include prevention components within the protocols and link them with initiatives from other ICDs involved in related efforts.

Current Status

NHLBI continually reviews its ongoing studies of the cardiopulmonary and hematologic complications of HIV infection and has developed initiatives that include prevention components as listed below. In addition, NHLBI has a long history of collaboration with other ICDs in AIDS research. These collaborations have included two programs studying HIVIG with NIAID and

NICHD, two programs studying the effect of HIV on the bone marrow with NIDDK, and two programs studying the effect of HIV on the lung with NIAID. NHLBI is currently developing with NIAID a Phase I study of the safety and pharmacokinetics of thrombopoietin in HIV infection.

Future Actions

NHLBI intends to fund a program in FY 1997 that will support the development and subsequent study of monoclonal antibodies in an effort to prevent maternal-fetal transmission of HIV-1 and slow disease progression. NHLBI also will provide funds in FY 1997 that will support development of new testing procedures which detect early infection prior to antibody formation. These tests could potentially be used to design therapeutic trials to interrupt transmission at an early stage. Also planned for FY 1998 is a PA that would request applications proposing research on the use of gene therapy with hematopoetic cells. These cells, which may in part provide a sanctuary for HIV infection, could be made resistant to HIV infection and be used to reconstitute the immune system of HIV-infected individuals. Another PA targets applications proposing to study the immune defenses of the lung and to develop interventions that would interrupt OIs.

Recommendation 80, Part 3

Accelerate plans to publicize the availability of potentially valuable biologic materials in repositories from studies of transfusion-associated HIV infection.

Current Status

NHLBI has already accelerated plans to avail outside investigators of the valuable biological samples in the repository. As part of this effort, NHLBI convened a working group to address the problems of informed consent for a repository where much of the research plan is unknown at the time the sample is retrieved from the donor. At that meeting, NHLBI developed a generic consent form to be used in the future for patients whose samples will be included in the repository. At the present time, NHLBI also is developing a plan for appropriate review of such research objectives in order to ensure that samples are used only for highly meritorious research programs. In response to this recommendation, NHLBI has developed a pamphlet for dissemination and is developing a program so that a detailed description of the cohorts whose blood specimens are stored in the repository can be available to highly qualified investigators through the NIH home page on the Internet.

C. National Institute of Child Health and Human Development (NICHD)

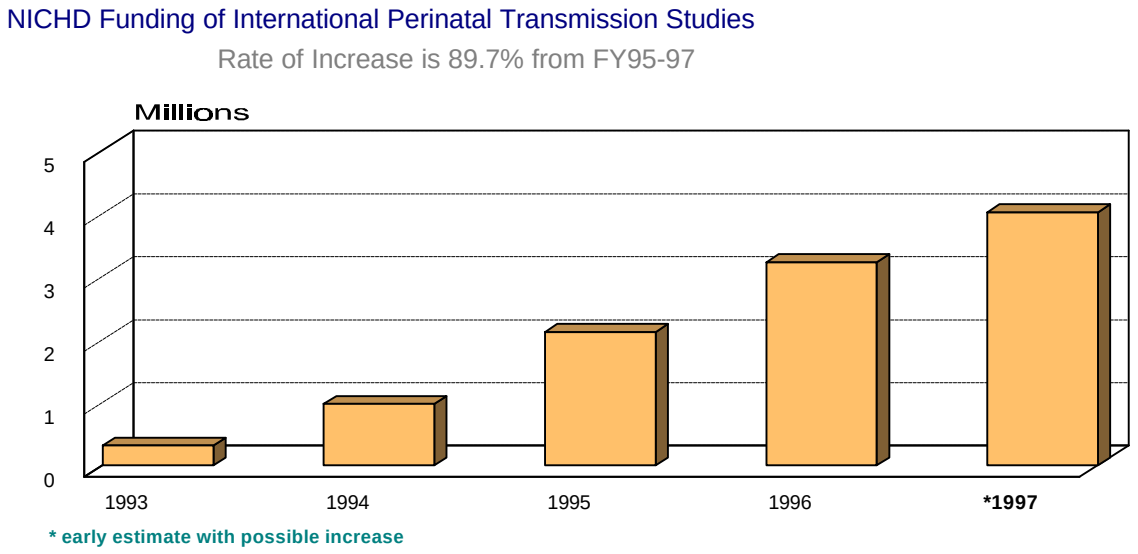
Recommendation 81 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 30, Nos. 1–2]

Recommendation 81, Part 1

Shift perinatal HIV resources from domestic transmission studies to international prevention studies.

Current Status

NICHD is fully committed to supporting international research efforts to prevent perinatal HIV transmission as demonstrated in its expenditure history. Over the past 5 years, NICHD has allocated increasingly more resources to international studies targeted to preventing perinatal HIV transmission. For example, research opportunities have already allowed the NICHD to increase its funding support for international perinatal HIV studies by approximately 90 percent between FY 1995 and 1997. (The FY 1997 dollar amount indicated on the graph below is a conservative estimate representing only the resources already committed. NICHD FY 1997 funding likely will exceed this estimate.)



Current NICHD-supported international studies aimed at preventing mother-to-fetus/child transmission of HIV infection are based on knowing what studies are ongoing or planned in both the international and domestic setting and what types of prevention strategies are feasible in settings where health care resources are scarce. These considerations have resulted in a carefully balanced portfolio with a range of international studies appropriate to the scientific research opportunities and public health needs. For example, NICHD currently funds intervention trials in Malawi, Uganda, Kenya, Thailand, and Tanzania. If proven effective in preventing HIV

transmission from mother to fetus/child, the intervention strategies will become widely available to other developing countries.

NICHD actively participates in HIV perinatal transmission working groups sponsored by the WHO and the NIAID-sponsored HIVNET to explore future research opportunities. NICHD uses these working groups to identify emerging opportunities to support international research opportunities focused on perinatal HIV transmission by becoming aware of planned activities, helping to identify gaps and overlaps in research efforts, and helping to develop research priorities.

Future Actions

NICHD will continue to closely monitor this area of research and work with the scientific community. Attention will be given to ensuring that there is an appropriate balance of resources between domestic and international perinatal transmission and intervention studies. This effort should result in a carefully planned approach to studying ways to interrupt vertical transmission. Continued discussions with the NIAID, international groups, and nongovernmental advisors will allow NICHD to take full advantage of international opportunities as they develop. For example, the NICHD is structuring a meta-analysis of 10,000 infant pairs from the United States and European nations to develop a unique new data set to look at obstetrical manipulations (including Cesarean section) and their impact on vertical transmission of HIV. Issues associated with NICHD efforts to support international research on preventing HIV maternal-fetal transmission include the following:

- The developing world is heterogenous. Interventions ranging from very simple and inexpensive to the moderately high tech and expensive must be evaluated.

- Interventions are not yet fully established in the domestic arena. For example, the fetus/infant of an HIV-infected pregnant women with advanced disease may not benefit from the ACTG 076 regimen. The role of newer drugs, of vaccines, and of combination therapies in preventing perinatal HIV transmission is unknown. When more AZT resistance occurs, alternatives to the ACTG 076 regimen must be in place.

- What research should be supported (whether domestic or international) hinges on issues of scientific opportunity, new discoveries, feasibility, and a number of other factors. Neither an artificial percentage of research funds nor an arbitrary designation of “more” can be decided in advance of scientific opportunity or advances.

Recommendation 81, Part 2

Increase the use of experimental trials and multicenter collaborations to evaluate the influence of contraceptives on STD/HIV transmission. Utilize the contraceptive clinical trials network and RCTs where feasible.

Current Status

With reproductive health an important part of its mission, NICHD has long supported pre- and post-marketing research and development and evaluation studies of new and existing contraceptives. Given the critical public health needs to provide women with a variety of effective and acceptable means to prevent both pregnancy and STDs, NICHD has increased efforts to develop and examine new and existing contraceptives for their efficacy in preventing STD/HIV transmission. Other studies have targeted the efficacy of various modes of delivery or application of contraceptive drugs, as well as consumer preferences concerning different types of products, and undesirable side effects that inhibit use of the products or possibly increase susceptibility to HIV infection. NICHD continues to support studies of SIV transmission in nonhuman primates to better define human heterosexual HIV transmission and its prevention. NICHD has used different funding mechanisms, including RFAs, to encourage new and innovative research applications in the reproductive sciences. NICHD also is initiating the Contraceptive Clinical Trials Network. Recent research findings, such as those concerning vaginal changes induced by different products, highlight the continued need to use a variety of mechanisms to further research in this area.

Future Actions

NICHD is committed to pursuing research to evaluate the influence of contraceptives on STD/HIV transmission. Some current and planned implementation steps are outlined below.

- The female condom was added as an intervention in the only existing prospective observational multisite study of women using barrier contraceptive regimens for preventing STDs. Results will allow scientists to compare efficacy of the male condom versus a female condom.

- NICHD intends to complete its review of applications in response to an RFP entitled "Efficacy Trial of Spermicidal Agents." Awarded projects will examine the contraceptive efficacy of spermicides used alone, focusing on consistent and correct usage as well as average usage. Results will help define which formulations of N-9 provide the best contraceptive efficacy, cause the least amount of mucosal irritation, and are the most preferred. Results will help estimate the product's potential to prevent STD/HIV infection. NICHD plans to make awards in the summer of 1997.

- In FY 1997, NICHD will develop and refine activities on understanding the properties of vaginal agents that may have an effect on STD transmission.

- NICHD will propose the establishment of a joint NICHD/NIAID task force on the development and evaluation of microbicides/spermicides.

- NICHD plans to examine the efficacy and acceptability of new condoms made from synthetic polymers.

D. National Institute on Drug Abuse (NIDA)

Recommendation 82 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 31, Nos. 1–2]

Recommendation 82, Part 1

Take a leading role in conducting and coordinating programs of research on ways to prevent HIV by facilitating access to sterile syringes, on the social ecology of parenteral HIV transmission, and on social-structural or policy factors that may affect initiation of drug injection.

Recommendation 82, Part 2

Investigate interactions of drug and drug-related behaviors on viral type, viral load, and shedding in order to determine the effects on transmission and disease progression in HIV-infected drug users.

Current Status

The NIH responses to Recommendations 66 through 69 address the issues regarding needle/syringe access and factors associated with needle/syringe use.

It should be further noted, however, that NIDA is conducting research on social factors related to drug injection. The concept of social networks provides an understanding of the effect of relationship organization structures on the dynamics of HIV transmission. Network-based research has been a mechanism for studying the epidemiology of HIV, recruiting subjects for intervention trials, and delivering HIV interventions. Network studies have reported that HIV risks vary by network size and composition and by the roles and relationships among network members. For example, it has been shown, in low seroprevalence areas, persons most likely to be HIV-infected are isolated groups and individuals weakly connected to networks. With respect to interventions, it has been shown that network leaders are effective in disseminating AIDS knowledge and resources and changing network norms about reuse of syringes.

Social-structural and network analysis also is used to understand the relationship of drug users to other populations/groups and to understand the course of the HIV epidemic. For example, out-of-treatment drug users may act as bridges of infection from one population group to another: networks of male prostitutes who use drugs have been shown to act as bridges of infection between one population group and others at risk for HIV infection. Through a number of extant PAs, NIDA encourages investigators to take a network-based approach to the study of HIV risks and to deliver HIV interventions in an efficient manner (e.g., PA96-074 “Drug Use, Sexual Behaviors, and HIV in Men”; PA95-083 “Women’s HIV Risk and Protective Behaviors”; PA95-057 “HIV Risk Behaviors, Determinants, and Consequences”; and PA94-054 “Strategies To Reduce HIV Sexual Risk Practices in Drug Users”).

E. National Cancer Institute (NCI)

Recommendation 83 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 33, Nos. 1–3]

Recommendation 83, Part 1

Focus on epidemiologic research of AIDS-related and retroviral-associated cancers.

Current Status

The NCI research program on the epidemiology of AIDS-related and retroviral-associated malignancies includes molecular epidemiologic studies of immunologic and virologic precursors of cancers, markers of host genetic susceptibility, early markers of malignant transformation, early detection of neoplastic changes, prevalence and incidence of the full-range of cancers occurring in HIV-infected persons, and rapidity and natural history of malignant progression.

Beginning in 1994, the NCI allocated approximately $15 million annually to research on the epidemiology of AIDS-related and retroviral-associated cancers. The extramural portfolio is approximately $9 million and includes memoranda of agreement with NIAID and NICHD (see part three, below) to support natural history studies of AIDS-associated cancer in men and women. NCI's extramural portfolio also has included a group of investigator-initiated research grants to study the natural history of cervical neoplasia in HIV-1- and HIV-2-infected individuals, the natural history of the human papillomavirus (HPV) as it is associated with anal and genital neoplasia, the natural history of human T-cell leukemia virus-I (HTLV-I) infection, and the epidemiology of pediatric HIV-related lymphomas. Additional studies have been approved and submitted for funding in the areas of molecular epidemiology of non-Hodgkins lymphoma (NHL) and Kaposi's sarcoma (KS). The extramural portfolio in this area has been targeted for growth, and an updated PA is forthcoming.

NCI's intramural research program in the epidemiology of retroviral and AIDS-related cancers is unique among NIH programs. Its goal has been to study "the unusual, the important, or both" on a large scale, in a way that extramurally funded research cannot. Examples of important research innovations already produced by this program include predicting future trends in the United States AIDS epidemic, assessing the role of vaginal virucidal washes in prevention of perinatal HIV transmission, and finding that KS tumors are clonal and that chromosomal translocations may be the precursors of NHL. This program focuses increasingly on surveillance of AIDS and cancer prevalence, using the multistate AIDS-Cancer Match Registry; e.g., in exploiting existing repository collections to study intermediate markers of cancer risk in the presence of HIV infection. This program also uses the Multicenter Hemophilia Cohort Study, e.g., in continuing research on the natural history of HIV infection and determining the latent period of related cancers.

Recommendation 83, Part 2

As opportunities develop, pursue intervention research with other groups within and outside of the NIH that already have established the necessary multidisciplinary research teams.

Current Status

As suggested, successful collaborations have been established in this area, including (1) the Malawi studies of vaginal antibacterial washing during labor, which was found to protect the infant from HIV transmission when membrane rupture occurs several hours before delivery; (2) the study which found that vitamin A supplementation of pregnant females reduces the likelihood of perinatal transmission; and (3) studies on transmission through breast-feeding. All of these studies have been important in identifying means of intervention that can be employed to minimize spread of HIV infection. Other collaborative intervention research projects currently being developed include the banking of specimens from the WIHS within the AMC program and exploration of the potential for conducting treatment trials of cervical intra-epithelial neoplasia within the WIHS in conjunction with the Gynecologic Oncology Group.

Recommendation 83, Part 3

Actively pursue expanded linkages to cohorts funded by other ICDs to maximize opportunities to study HIV-associated malignancies.

Current Status

The Panel recommendation has already been implemented with important successes. The MACS Malignancy Program, initiated in 1987, has provided continual support to four clinical sites and the data center to develop and maintain common surveillance instruments to study the occurrence, distribution, and determinants of HIV-associated cancer; to maintain an autopsy program and related tissue repository for use in pathogenesis studies; and to facilitate high-priority pilot studies of HIV-related malignancies within this study of the natural history of HIV infection in approximately 5,000 men who have sex with men. MACS samples have been used to identify human herpesvirus 8 (HHV-8) as the likely etiologic agent of KS. Greatly elevated levels of soluble CD23, a B-cell stimulatory factor, have been identified in a retrospective study of HIV-seropositive MACS participants who subsequently developed NHL. Other analyses have identified persons at very high risk for developing KS, trends in KS as an AIDS-defining event, and behavioral factors associated with NHL. Currently, NCI intramural investigators are collaborating with MACS investigators on studies of host genetics in HIV infection and disease progression. In 1996, NCI awarded approximately $700,000 total costs to the MACS, with similar levels of support tentatively identified for FY 1997-1998 (leading up to the MACS recompetition in FY 1999).

In 1995, NCI established the WIHS Malignancy Program, providing approximately $700,000 in 1995 and again in FY 1996 to support research on the role of HHV-8, also known as

KS-associated herpesvirus (KSHV), in the pathogenesis of AIDS-related malignancies and to fund HPV typing of cervicovaginal lavage specimens within this natural history study of HIV infection in approximately 2,500 women, three-quarters of whom are women of color. Of particular note is the relationship the WIHS already has established with the NCI AMC, including utilizing the AMC tissue banks as a repository for WIHS specimens.

Future Actions

Under discussion is the potential for nesting clinical treatment trials of cervical intra-epithelial neoplasia within the WIHS, in conjunction with the Gynecologic Oncology Group and the AMC infrastructures. Future NCI plans for the WIHS, in addition to providing ancillary support intended to lead to investigator-initiated research projects, include continuing to provide supplementary funding to the WIHS to foster the WIHS AIDS Malignancy Research Agenda. If such an arrangement occurs, it is anticipated that the NCI-WIHS clinical site will become the focus of AIDS-malignancy research in women, particularly molecular epidemiologic studies and possibly intervention trials.

F. National Institute of Mental Health (NIMH)

Recommendation 84 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 35, Nos. 1–2]

Recommendation 84, Part 1

> *In collaboration with behavioral and social scientists, continue the spectrum of research from observational studies to randomized controlled trials directed at primary prevention of HIV transmission, with an emphasis on targeting special at-risk populations, maintaining of behavior change, and assessing of both biological as well as behavioral outcomes.*

Current Status

NIMH has supported behavioral epidemiological studies of diverse populations in order to identify the distribution of high-risk HIV-related behaviors. Studies of knowledge, attitudes, and behaviors of at-risk populations also have been undertaken. The data from these two research strategies have been used to develop behavioral AIDS prevention programs.

Even though many of these studies have used different procedures, HIV-related risk criteria, and assessment methods and are based on small numbers of study participants, these projects have demonstrated that face-to-face interventions at different levels of intensity tailored in sample-specific ways can produce substantial reductions in participants' high-risk sexual behaviors.

Reaching definitive conclusions about the efficacy of behavior change intervention models (e.g., determining populations with whom the interventions work, generalizing across settings and sites, and establishing intervention efficacy apart from potentially idiosyncratic "intervenor" and setting characteristics) will be most convincingly established by data from a multisite controlled

clinical trial. NIMH has made a major commitment to a seven-site Phase III multisite study with both biologic and self-report outcomes that will be unblinded in May 1997.

Future Actions

The effort to expand tested interventions to different institutions, populations, and geographical areas will be accelerated. NIMH intends to expand its research effort to design and assess the effectiveness of mental health and HIV prevention programs integrated into mental health treatment programs in stemming the rise of HIV infection in persons with mental illness. In collaboration with NIDA and NINR, NIMH has taken the lead in developing a PA on "Preventing Relapse to High-Risk HIV Behaviors" to solicit grants on maintaining behavior change.

In collaboration with other ICDs, NIMH will initiate research that characterizes various behavioral risk factors and assesses how these risk factors combine to determine the degree to which a person is at risk for HIV infection. Special attention will be paid to the relationship between these risk factors and how individuals evaluate their level of risk and self-label (e.g., gay, bisexual, heterosexual). This has important implications for the validity and reliability of self-report measures.

A special population at high risk is the severely mentally ill. NIMH (with OAR Discretionary Funds) supplemented 10 grantees working with this population. A special AIDS risk behavior assessment will be included and preventive interventions designed in this program.

NIMH will work with other PHS agencies to conduct controlled prevention trials to develop and evaluate interdisciplinary intervention models tailored to diverse settings (e.g., prisons, workplaces). The tested interventions will be integrated into ongoing health programs, such as STD and TB clinics and mental health and primary health care agencies. NIMH also is collaborating with NIAID on the design and implementation of behavioral protocols with the HIVNET cohorts. Efforts will address scientific questions associated with designing appropriate interventions that assess HIV seroincidence that could be used in future vaccine trials.

The NIMH Multisite HIV Prevention Trial will unblind its results in 1997. As the virus is invulnerable to international borders and the increasing global economy is leading to increased social interactions among citizens of all countries, a major multinational prevention program adapting the Multisite protocol to international sites will be expanded in order to test it with multiple populations and in multiple geographic areas, assuming the results of the original trial are favorable.

Recommendation 84, Part 2

> *In collaboration with behavioral and social scientists, expand current research on social and behavioral factors that affect the rate of HIV disease progression, especially among persons with unusual HIV outcomes.*

Current Status

Some persons experience a long time between infection with HIV and a diagnosis of AIDS while others experience a more rapid transition to a symptomatic stage of HIV disease. Interventions are needed to slow disease progression and extend activities of daily living and improve quality of life in these persons.

While the biomedical community continues to seek more effective treatments and vaccines for HIV disease, the psychosocial needs of people with HIV disease also must be met. Many patients cannot cope with the psychological reality of the disease. For some, maladaptive coping includes not adhering to the recommendations of their physicians and other health care providers, resulting in a diminished quality of life that jeopardizes their emotional, physical, cognitive, or economic functioning. However, scientific data currently under assessment suggest that personal resilience and effective behavioral and cognitive strategies can reduce the stress that often accompanies HIV infection and can have a palliative effect on the progression of the disease.

Future Actions

An expanded NIMH research program, in collaboration with NINR and other ICDs, will be directed at further extending the asymptomatic stage of HIV and improving the quality of life of persons living with AIDS. Research initiatives will be implemented to examine whether prevention interventions can also extend the asymptomatic period. In addition, an evaluation will be made to determine whether coping techniques that enhance psychological functioning also augment health behavior, reduce AIDS risk-related sexual activity, and affect HIV disease progression. Studies will be supported to examine the social and cognitive processes in illness behavior using a theoretical framework, such as the self-regulation model of illness behavior. The focus will be on the appraisal process involved in making judgments of perceived health threats under a variety of conditions. Among the possible determinants of health-related judgments to be studied are diagnostic status, affect, and social influence. These latter studies will derive and test predictions from a theory, such as social comparison theory, to extend the study of illness cognition to social interaction processes.

Effective prevention strategies require the cooperation and support of infected individuals and their integration into adaptive social support networks—factors that are adversely affected by psychological distress and poor mental health functioning. Therefore, research will be supported to determine new ways to strengthen social ties of HIV-infected people and to encourage the participation of informal caregivers.

The stigma experienced by many HIV-infected people impels some to withdraw socially, beginning a cycle of isolation and depression. NIMH has been supporting a national public opinion survey that has identified the prevalence of stigmatizing attitudes and beliefs toward HIV and AIDS among the U.S. adult population (e.g., in ethnic and racial groups and in various age groups) and shown how that prevalence of stigma has changed over time. In order to implement this recommendation, NIMH will encourage the use of this important database by NIH investigators to support research projects that test interventions designed to overcome consequences of social stigma associated with HIV infection and AIDS.

G. Fogarty International Center (FIC)

Recommendation 85 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 36, No. 1]

> *The FIC program warrants continued support in establishing linkages between U.S. universities and scientists in other countries for prevention research. Increased support linked to a U.S. institution is needed for reentry research funding for high-caliber trainees.*

Current Status

FIC is committed to the support of the AITRP and has included it in its long-range planning process. In addition, FIC has had discussions with OAR concerning future directions for AITRP. In consultation with OAR, FIC convened a nongovernmental panel in October 1996 to review the AITRP. A preliminary review of the draft report from this review indicates that the review panel strongly endorses the AITRP and makes several recommendations that FIC will incorporate in planning the next 5-year funding cycle.

FIC has already taken important steps to implement the Area Review Panel's recommendation concerning support of high-caliber trainees for reentry research funding. Beginning in FY 1993, the sixth year of the AITRP, FIC substantially expanded a relatively new feature of the program, "Advanced In-Country Research," to provide continued research support for talented international scientists upon completion of their training and return to their home countries. This feature facilitates the ability of former trainees to effectively utilize the new scientific skills they have obtained under the program and to maintain research collaborations with their U.S. colleagues through the conduct of collaborative research. This feature has proven to be an important component of the AITRP and has enabled the program to reach a high level of research productivity, as evidenced by articles authored or coauthored by current and former trainees in leading peer-review journals. Advanced in-country research will continue to be a significant component of AITRP.

Future Actions

FIC will include this activity in the RFA for the AITRP recompetition, which is expected to be released in 1997.

V. SPECIAL ISSUES

A. Funding Mechanisms—Extramural and Intramural Research

Recommendation 86 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 38, No. 1]

Continue OAR and ICD support of directed types of funding mechanisms in the area of natural history and epidemiology, particularly the use of cooperative agreements in the areas where central coordination is necessary. Directed funding should be provided for research in high-priority areas where intellectual or financial incentives are not sufficient to attract significant scientific interest.

Current Status

NIH agrees with the recommendation to continue support of directed types of funding mechanisms in the area of natural history and epidemiology. Natural history cohort studies must be funded by directed types of funding mechanisms because it is extraordinarily difficult to fund large, multicenter, multidisciplinary studies via R01s or RPGs. These cohort studies have long-standing policies that invite collaboration with basic scientists who then utilize the collected and well-characterized biologic samples from the cohort studies to address basic questions of etiology and pathogenesis.

There are a number of cohort studies on the natural history of HIV infection in designated populations ongoing with NIH support. The MACS investigates the natural history of HIV infection and disease in gay men at high risk of infection in the United States. The WITS investigates the natural history of HIV infection and disease in pregnant women and in children infected through vertical transmission. The Hemophilia Growth and Development Study examines the natural history of HIV infection in children and young men infected by the use of contaminated blood factor products. The WIHS investigates the natural history of HIV infection and disease in women and looks particularly at gender-specific problems caused by HIV infection. The Adolescent Medicine HIV/AIDS Research Network is funded by a cooperative agreement that studies the spectrum of disease in adolescents infected through the use of contaminated drug injection equipment or through heterosexual or homosexual intercourse.

Future Actions

NIH will continue to support productive natural history and epidemiology cohort studies using these directed mechanisms. NIH will seek the advice of the PSWG of the OARAC and other similar groups to identify additional high-priority areas that may require commitment of additional resources.

Recommendation 87 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 38, No. 2]

Provide support and oversight for the Centers for AIDS Research programs that include biomedical, clinical, laboratory, and prevention science research.

Please refer to the NIH responses to Recommendations 40 and 41.

Recommendation 88 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 39, No. 3]

Facilitate collaboration among NIH intramural and NIH extramural epidemiologists.

Current Status

Current NIH activities facilitate the collaboration among NIH intramural and extramural epidemiologists through, for example, the NIH Epidemiology Interest Group. This interest group meets routinely, bringing together NIH epidemiologists to present and discuss new research and to identify new scientific questions and directions.

The OAR Coordinating Committee on Natural History and Epidemiology is one of six coordinating committees within the OAR and has both intramural epidemiologists and extramural epidemiology program staff as committee members. This committee is responsible for the development and annual update of the natural history and epidemiology portion of the annual NIH Plan for HIV-Related Research.

Future Actions

New and expanded opportunities will be pursued to facilitate increased communication and collaboration between intramural and extramural epidemiologists. The following groups will play critical roles in these efforts:

- The NIH AIDS Interest Group. Originating with the Director of OAR in collaboration with the Director of NIAID, this group had its first administrative/planning meeting September 30, 1996. This interest group will provide new and expanded opportunities for NIH intramural and extramural epidemiologists, as well as all other NIH AIDS scientists and program staff, to interact and collaborate in future and ongoing research activities.

- The NIH Epidemiology Interest Group. The current Epidemiology Interest Group has recently merged with the Clinical Trials Interest Group and will facilitate expanded contact and collaborations.

B. Peer Review

Recommendation 89 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 39, No. 1]

Restructure an existing IRG to create a study section devoted to prevention science research.

Please refer to the NIH response to Recommendation 8.

Recommendation 90 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 39, No. 2]

Increase the interaction between prevention science NIH extramural program staff and existing IRGs so that program research priorities are understood more fully.

Current Status

NIH agrees that additional interaction by DRG and ICD representatives on OAR committees with nongovernmental scientists serving on these same committees should be encouraged to provide continuing updates on DRG practices and ICD AIDS priorities.

Program priorities may be affected through selection of applications to be funded, which is a responsibility of extramural program staff. Mechanisms already exist whereby NIH extramural program staff may communicate their research priorities to the scientific community, including IRG members (e.g., through PAs, RFAs, RFPs, and the NIH Web site). These program priorities should be made available to the SRAs on a routine basis so that they may forward or distribute the priority statements to the members of their IRGs outside of the actual meetings of the IRGs.

Please refer to NIH responses to Recommendations 2–6, 130–31, 335, 340, and 352.

Recommendation 91 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 39, No. 3]

Consider alternatives to the usual designation of a primary and secondary reviewer when a project is highly multidisciplinary.

Current Status

NIH concurs with the Panel recommendation that alternatives to primary and secondary reviewers should be explored for multidisciplinary projects. The DRG policy dictates that SRAs assign as many reviewers as necessary to provide sufficient expertise for each application reviewed. At a minimum, this requirement means at least three persons: two reviewers and one discussant. In the case of multidisciplinary applications, the need to have more than three persons assigned is

clear, and DRG SRAs have the flexibility to consider alternatives (e.g., more than three assigned committee members or outside consultants).

Future Actions

The SRAs will continue to strive to match a multidisciplinary science application with a comparable multidisciplinary team of reviewers who are familiar with both the science and the strengths and the weaknesses of the multidisciplinary approach.

Recommendation 92 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 39, No. 4]

Improve mechanisms for peer review of research proposals funded by master contracts, such as the HIVNET.

Current Status

NIAID agrees with the Panel that peer review of research supported by master contracts should be of the same caliber as the grant peer-review process. In 1996 NIAID/OAR cosponsored the review of the HIVNET program. The HIVNET review mechanism and its selection of subcontracts were evaluated and found to be appropriate. The panel recognized the improvements that already have been implemented since the NIH AIDS Research Program Evaluation Task Force report had encouraged further refinement. Review staff from the NIAID are providing greater guidance and oversight of the peer reviews organized and conducted by the master contractor. Additional depth of scientific expertise has been included in review panels. The master contractors are required to adhere to the same guidelines and regulations for composition and conduct of peer-review groups as NIAID.

Future Actions

NIAID will continue to provide oversight of the peer-review process being conducted by the master contractors to ensure that qualified scientists are included in the review panels and that proper procedures are followed.

C. Cross-Institute and Interagency Collaborations

Recommendation 93 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 40, No. 1]

Commit to expanding and strengthening collaboration among ICDs within the NIH and among other Federal agencies.

Current Status

NIH strongly supports the Panel recommendation. There are a number of mechanisms by which collaboration among ICDs within NIH is actively encouraged by the OAR. The Coordinating Committees provide the opportunity to address trans-NIH science priorities in the context of developing the annual NIH Plan for HIV-Related Research. In some instances, the Coordinating Committees also engage in sponsoring scientific discussions that cut across the ICD missions. Similarly, NIH Interest Groups have afforded an opportunity for exploring possibilities for cross-ICD collaboration and cooperation. In addition, ICDs have forged collaborations among themselves and with other Federal agencies on a number of RFAs and specific projects by cofunding such initiatives as the Add-HEALTH and the HIV Cost and Services Utilization Study (HCSUS). NIDCD recently began a cooperative clinical study with the U.S. Air Force on sensorineural deficits in HIV-infected active duty and retired military personnel. It is important to expand these collaborations and to encourage more formal expressions of jointly sponsored projects and activities as NIH continues to move into the area of prevention science.

Since the Task Force report was issued, OAR has worked with the ICDs to facilitate additional collaborations. For example, with OAR's assistance, program staff and grantees funded by NIDA, NIAAA, and NIMH have been collaborating with NIAID and its grantees in developing specific trials of behavioral interventions that will be tested in the HIVNET program.

Future Actions

Further ICD collaboration will be encouraged through the development of the NIH Prevention Science Plan. As part of that process, the OARAC's PSWG includes *ex officio* representation from the CDC. NIH Institutes will continue their ongoing relations with other DHHS agencies (e.g., CDC, the Substance Abuse and Mental Health Services Administration [SAMHSA], and HRSA) and continue to cosponsor activities when appropriate.

D. Cross-Disciplinary Research: Overlap With Other Panels

Recommendation 94 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 40, No. 1]

Extend the collaboration developed within the framework of the Area Review Panels to include the activities of the five OAR Coordinating Committees.

Current Status

Currently, there are six OAR Coordinating Committees. Although there is meaningful overlap among some of them with respect to the scientific areas addressed, for example Natural History and Epidemiology and Behavioral and Social Science Research, there has not yet been any formal procedures developed for collaboration. At the same time, the OAR chairs of the respective committees have made an effort to inform each other of relevant activities and issues, and members of the Coordinating Committees work together on a daily basis. In addition, the

construction of the Prevention Implementation Group for the purpose of writing this response document provided a model for linking these committees.

Future Actions

Further collaborations among the Coordinating Committees will be encouraged during the FY 1999 planning process. The Committees will be consulted about the optimal mechanisms for crafting these, including such possibilities as establishing liaison positions between committees and convening joint meetings between two or more committees on topics of mutual interest.

E. Links Among Research, Services, and Communities

Recommendation 95 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 41, No. 1]

Extend the CAB models developed for clinical trial networks and cohort studies to include community involvement in the area of prevention science research.

Current Status

NIAID has had a longstanding commitment to community involvement in all aspects of its AIDS research efforts. The Institute welcomes the endorsement of the Area Review Panel for continued and enhanced interactions with the AIDS community and those at risk of HIV infection.

NIAID has solicited community input to its research efforts through formation of local and national community advisory boards (CABs), participation of CAB members in governing bodies of research groups, inclusion of community members on all of the program review panels, and participation of community members on NIAID advisory committees such as the National Advisory Allergy and Infectious Diseases Council and ARAC. In addition, the Institute has encouraged community participation in NIAID-sponsored scientific meetings by providing travel funds. All major clinical trials groups, natural history cohort groups, and vaccine and prevention trials groups have organized CABs.

In addition to NIAID's CABs, other ICDs have funding mechanisms for integrating community involvement into HIV prevention research. NIMH's AIDS Research Centers, for example, are required to have a community board and to engage in active community participation and information dissemination activities and strategies. This community participation includes preparing detailed assessment and treatment manuals; providing consultation to agencies and groups seeking to develop research in this area; preparing information on prevention strategies; and participating and taking leadership roles in workshops, conferences, and meetings designed to share established research methods and knowledge with other researchers and interested agencies and community groups.

Future Actions

NIAID recently organized a program review to evaluate the effectiveness of the national CABs for its various cohort and clinical groups. Recommendations from that panel will be presented to the ARAC in 1997. NIAID will continue to support the local and national CABs associated with its cohorts and trial groups, including those engaged in prevention research. In addition, NIAID will work with the CABs to implement the recommendations of the NIAID program review panel.

F. Links Between the Public and Private Sectors

Recommendation 96 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 42, No. 1]

Proactively collaborate with private donors and other sources of venture capital to stimulate biotechnological development.

Please refer to the NIH response to Recommendation 31.

Recommendation 97 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 42, No. 2]

While exploring the AIDS research opportunities offered by private organizations, NIH should critically evaluate the efficiency and scientific productivity of master contract mechanisms.

Current Status

NIH approval for use of the master contract mechanism requires specific justification. Master contracts are not widely used at NIH; however, they offer a certain level of flexibility to handle variable workload in multisite epidemiology studies, in clinical trials, and in preclinical studies of biomedical products in nonhuman primates. This mechanism offers NIH the ability to rapidly expand the size of projects and to select project sites from a larger set of prequalified applicants. It has been used to support HIVNET's domestic and international activities, and the issue of its efficiency and productivity was raised in the HIVNET program review conducted in June 1996. The review panel found the master contract to be acceptable and appropriate for HIVNET.

Future Actions

All master contracts are peer reviewed on a regular basis, consistent with timely renewal of existing project activities. Criteria for efficiency and scientific productivity have been and will continue to be included in such reviews. Every effort will be made to utilize RPG mechanisms where complex grant mechanisms, such as cooperative agreements, are equally appropriate.

G. Access and Ownership of the Products of NIH-Supported AIDS Research

Recommendation 98 [Natural History, Epidemiology, and Prevention Research ARP Report, p. 43, No. 1]

Streamline and coordinate mechanisms for access to existing repositories of data and biomedical specimens, while emphasizing the need for qualified scientists not funded by the primary research network to work closely with epidemiologists and other scientists working within the research network.

Please refer to the NIH response to Recommendation 42.

Behavioral, Social Science, and Prevention Research Area Review Panel Recommendations

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INTRODUCTION

Recommendation 99 [Behavioral, Social Science, and Prevention Research ARP Report, p. 8, No. 1]

Support for Behavioral, Social Science, and Prevention Research should be increased substantially to at least double its current level. This, in turn, should be allocated according to the scientific priorities identified in the annual update of the NIH Plan for HIV-Related Research.

Current Status and Future Actions

NIH is committed to vigorously supporting highly meritorious research in the behavioral, social, and prevention sciences. It is anticipated that resources for this area of HIV/AIDS research will continue to increase over the next several years. On the other hand, an arbitrary target of a doubling of support over a particular time interval may not represent a realistic approach. Rather, linking funding levels to opportunities to conduct high-quality research that responds to the needs posed by the HIV/AIDS epidemic has the potential to make major contributions to preventing HIV transmission and ameliorating the consequences of HIV and AIDS. The recommendations emerging from the PSWG of the OARAC will be particularly helpful in guiding NIH levels of support in different areas.

Recommendation 100 [Behavioral, Social Science, and Prevention Research ARP Report, p. 8, No. 2]

The Panel recommends that OAR take a leadership role, using its Coordinating Committee mechanism, to ensure that the scientific priorities identified for AIDS-related behavioral and social science research at the NIH are responsive to the recommendations of this report, and that as newly emerging issues are identified, research is initiated to address them. The Coordinating Committee should include external (non-NIH) members and be used to stimulate trans-ICD and trans-disciplinary activities. Examples of such activities include developing joint Request for Applications (RFAs), establishing lead agencies for specific priorities, and establishing coordination with other PHS agencies (e.g., CDC, Substance Abuse and Mental Health Services Administration [SAMHSA], Health Resources and Services Administration [HRSA]).

Current Status

NIH and OAR are committed to ensuring that scientific priorities developed for NIH reflect the recommendations of this report. The Coordinating Committee on Behavioral and Social Science Research used the recommendations in the NIH AIDS Research Program Evaluation Task Force report to develop the priorities and strategies for the FY 1998 update of the annual NIH Plan for HIV-Related Research, and the Committee will again incorporate the Task Force report recommendations during the FY 1999 planning process.

The Coordinating Committees are charged with setting the scientific priorities for HIV-related research in their areas as part of the annual update of the NIH Plan for HIV-Related Research. These scientific priorities are identified through the regular activities and interactions of NIH staff with non-Government researchers and communities affected by HIV and AIDS. In addition, the priorities are reviewed and approved by the OARAC, which is composed of non-Government researchers and community representatives. Every attempt is made to ensure that the priorities and strategies articulated in the Plan reflect current developments in science and in the course of the HIV pandemic and that the Plan is responsive to recommendations issued in reports from such bodies as the National Commission on AIDS, the IOM, the National Academy of Sciences, and other groups that conduct reviews of AIDS research.

Future Actions

Coordinating Committee membership will remain confined to NIH staff, but the process of determining the specific priorities and strategies for behavioral, social science, and prevention research will continue to involve extramural researchers and community representatives to ensure scientific relevance and responsiveness.

Recommendation 101 [Behavioral, Social Science, and Prevention Research ARP Report, p. 9, No. 3]

> *The NIH, with collaboration from CDC, should establish sentinel stations in key areas throughout the United States that have different levels of seroprevalence. This can have multiple benefits, such as providing the ability to (1) monitor changes in risk behaviors, (2) identify new risk groups, (3) evaluate both naturally occurring and planned intervention efforts in a timely manner, and (4) conduct pilot intervention research for later development of R01s. (An underutilized mechanism, the P-30 Center grant, may be suitable for providing funds for this type of multisite undertaking.)*

Current Status

NIH agrees with the Panel that the ICDs and the CDC should coordinate and collaborate with each other in the communities where there is mutual interest and research activity. Sentinel stations in the United States can enhance NIH's ability to respond appropriately to the evolving course of the epidemic with respect to changes in dominant transmission modalities and incidence in demographic subpopulations. Some multisite prevention trials currently supported by NIH include sentinel functions as well as the prevention and evaluation functions addressed in this recommendation. However, many of the trials are not focused sufficiently on process level evaluation to assist researchers to appreciate the impact, over time, of "naturally occurring" and/or other agency-supported activities in the communities of interest. Rather, the trials are focused more on the planned interventions in the absence of other community efforts. The P30 mechanism could be useful for coordinating research projects being supported in the same communities by different ICDs and Federal agencies.

Future Actions

OAR and the ICDs will discuss this recommendation with the CDC to ascertain the best mechanisms for addressing it.

Recommendation 102 [Behavioral, Social Science, and Prevention Research ARP Report, p. 10, No. 4]

> *The OAR should develop guidelines, criteria, and a process for rating the AIDS-relevance of projects funded with NIH AIDS dollars. To implement this coding scheme, the principal investigator on a proposal should be required to prepare a brief rationale justifying the AIDS-relevance of the project if AIDS funds are expected to be used to support the project. The study section would be charged with determining whether the project met the criteria specified by the OAR.*

Current Status

NIH currently has in place guidelines and a process for rating the AIDS-relevance of projects funded with NIH AIDS dollars. Routine instructions given to PIs along with the standard grant application form (PHS 398; Rev. 5/95), request that applicants indicate "the importance and health relevance for the research described in this application. . . ." To ensure that AIDS-related projects are correctly identified, the application instructions specifically provide definitions for AIDS-relatedness: "(1) projects relating to the etiology, epidemiology, natural history, diagnosis, treatment or prevention of AIDS; (2) various sequelae specifically associated with the syndrome; and (3) preparation and screening of anti-AIDS agents as well as vaccine development." In the referral process, the PIs' responses to these instructions are considered seriously when accepting the application for the AIDS-expedited review and when assigning the application to the appropriate ICD and to one of the seven AIDS study sections. In the review process, the application is evaluated and scored on scientific and technical merit. The IRG will instruct the SRA to append an administrative note to the summary statement, should concern arise during review that the application does not fulfill the criteria for AIDS relatedness. In effect, current practices of grant application preparation and of grant assignment and review entail a continuous monitoring of the relevance of the application to AIDS research.

Future Actions

In addition to the process outlined above, as ICD-specific definitions of AIDS-related research are developed based on the NIH Plan for HIV-Related Research, these will be integrated into the current definitions presented in the instructions to applicants.

In addition, please refer to NIH responses to Recommendations 44–46.

Recommendation 103 [Behavioral, Social Science, and Prevention Research ARP Report, p. 11, No. 5]

> *The OAR should stimulate coordination among the NIH and other PHS agencies responsible for primary prevention and early intervention in HIV. This process should establish mechanisms for assessing, on a regular basis, the concerns of front-line HIV providers and integrating these concerns into the NIH research agenda.*

Current Status

NIH remains committed to fostering coordination and communication among the agencies of the DHHS that have responsibilities for primary HIV prevention and early intervention activities. NIH shares its research and research announcement information on a monthly basis with the other DHHS agencies through the HHS AIDS Coordinating Committee, which meets and routinely involves other agency representatives in research planning activities through *ad hoc* committees, cosponsored meetings, and other planning and information exchange vehicles. In addition, front-line HIV prevention and service providers, researchers, and HIV-infected and HIV-affected individuals and community representatives are involved in "think tank" meetings and conferences with NIH ICDs, other U.S. Government agencies, and foundations.

NIH sponsored a major conference in 1993 to enhance the understanding of HIV/AIDS information needs, resources, and services. This conference was attended by other representatives from U.S. Government agencies (i.e., CDC, VA, the White House Office of National AIDS Policy, HRSA, and SAMHSA) as well as non-Government scientists, health care providers, journalists, information specialists, and members of communities affected by HIV/AIDS. Among the positive results of this conference was the development of the annually updated "Guide to NIH HIV/AIDS Information Services," which serves as a "road map" for identifying various ICD HIV/AIDS responsibilities, efforts, and information sources, as well as identifying links to other PHS agencies, including the AHCPR, FDA, HRSA, SAMHSA, CDC, and the White House Office of National AIDS Policy.

HIV/AIDS information telephone services, such as the AIDS Clinical Trials Information Service (ACTIS) and the AIDS Treatment Information Service (ATIS), serve as central information and referral resources for information about federally and privately sponsored AIDS clinical trials and about federally approved guidelines on HIV/AIDS treatment. These services are supported by NIH and other PHS agencies.

One current NIMH project, funded in 1995 with OAR Discretionary Funds, is developing models of HIV/AIDS information dissemination through partnerships between behavioral and social scientists and community-based HIV prevention and service organizations.

Future Actions

The rapidly expanding fields of information technology and translational research provide new opportunities to coordinate and communicate efforts among the ICDs, other governmental and

nongovernmental agencies, communities, and individuals. NIH will expand its sponsorship of both domestic and international workshops and meetings designed to translate, disseminate, and coordinate efforts in the areas of HIV prevention and early intervention. These efforts will be further enhanced through a number of other vehicles including two existing OAR Coordinating Committees: Behavioral and Social Science Research and Information Dissemination, as well as the newly formed OARAC PSWG. As part of the development of an NIH-wide Prevention Science Plan, priorities related to information dissemination and community participation identified in the NIH Plan for HIV-Related Research will be considered. These include such topics as research on the cost-effectiveness of various interventions; the link between research and HIV prevention community planning; and issues of recruitment, retention, and adherence in clinical studies and access to new HIV prevention and treatment technologies by communities at high risk of HIV transmission.

Recommendation 104 [Behavioral, Social Science, and Prevention Research ARP Report, p. 11, No. 6]

The Panel recommends ongoing and increased NIH support for international efforts in Behavioral, Social Science, and Prevention Research through the spectrum of funding mechanisms used by the ICDs.

Current Status

NIH recognizes the importance of continuing and expanding its international efforts in HIV prevention science. NIH currently supports international behavioral, social science, and prevention research through a variety of mechanisms, including R01 research grants, the NIAID-supported HIVNET, and the FIC-supported AITRP. International social and behavioral research is conducted to determine the efficacy of behavioral interventions, as well as to study behavioral aspects of biomedical interventions. Other prevention research specifically examines potential biomedical interventions.

For the development of behavioral intervention strategies, NIH supports several specific international research projects including those studying (1) the impact of community-based outreach in decreasing high-risk drug-using behaviors among out-of-treatment drug users in Brazil; (2) the effect of peer counseling on high-risk behavior in Zimbabwe; (3) the effectiveness of peer education on HIV prevention among women; (4) the use of social networks in increasing condom use among military recruits in Thailand; and (5) the effectiveness of educational interventions for risk behaviors among truck drivers in Kenya.

Studies of vaginal microbicides are ongoing in Kenya and the Cameroon, and expansion of these types of studies were considered by NIAID and NICHD in collaboration with OAR at the end of calendar year 1996. Acceptability and other behavioral factors involving different products and formulations also were assessed. In addition, the role of community-based mass STD therapy in reducing heterosexual transmission is being studied in Uganda.

Studies are being conducted in Haiti, Thailand, and Uganda on modification of current protocols evaluating the use of AZT for prevention of mother-to-child transmission that may be more

appropriate for use in developing countries. Other studies of low-cost intervention strategies for the prevention of mother-to-child transmission include studies involving the use of vitamin A in Malawi, South Africa, and Tanzania; studies of HIV immunoglobulin in Haiti and Uganda; studies of vaginal cleansing and baby washing in Malawi; and studies of breast milk versus formula feeding in Kenya.

Future Actions

NIH is planning a workshop on international HIV/AIDS prevention research opportunities. This workshop will help to identify scientific opportunities in the areas of behavioral, social science, and prevention research. Of particular focus will be opportunities that address the interaction of behavioral and biomedical intervention strategies. The workshop also will identify potential opportunities for collaboration among the ICDs to cosponsor prevention research.

International scientific opportunities, including those identified at the workshop, will be considered during the development of the FY 1999 NIH Plan for HIV-Related Research as well as during the planning process for future years.

I. REVIEW OF BEHAVIORAL, SOCIAL SCIENCE, AND PREVENTION RESEARCH AT THE NIH BY SCIENTIFIC PRIORITIES

Recommendation 105 [Behavioral, Social Science, and Prevention Research ARP Report, p. 14, No. 7]

NIDA should support research that recognizes the diversity among the drug-using population (and their social networks) vulnerable to HIV. Relevant groups include homeless youth (the majority of whom are drug users), gay and bisexual drug users (especially IDUs), women at risk either through their own drug use or through sexual activity with drug users, including women who trade sex for money or drugs, and IDUs and crack smokers in the criminal justice system.

Current Status and Future Actions

NIDA has long recognized the importance of the diversity of drug-using populations and has supported research to understand and intervene with various groups at high risk for drug abuse and HIV. Vulnerable groups include those individuals who because of their drug-use and sexual behaviors are at risk of acquiring and/or transmitting HIV. The following groups are of particular importance to the HIV prevention research portfolio:

Women

NIDA is supporting basic social and behavioral research on women's HIV risk and/or protective behaviors combined with community-level intervention strategies aimed at understanding and preventing HIV/AIDS in women whose substance abuse practices and relational transactions put them at high risk of HIV infection. These include not-in-treatment IDUs; crack users; injecting and noninjecting sexual partners of male and/or female IDUs; and women who trade sex for drugs, money, or subsistence. Historically, these women have been omitted from research or have been difficult to reach and retain in research; hence, the knowledge base has often been limited to the male experience.

NIDA also is participating with NIAID and NICHD in both the WITS and WIHS, which are investigating the natural history of HIV in women and their infants. A large proportion of women in these cohorts have a history of current or former illicit drug use. Other NIDA-funded cohort studies of HIV are assessing gender differences in infection risk and progression factors.

NIDA has recently issued PAs for new research initiatives relating to "Women's HIV Risk and Protective Behaviors, Determinants, and Consequences"; "Strategies To Reduce HIV Sexual Risk Practices in Drug Users"; and "Women's HIV Risk and Protective Behaviors."

Drug-Using Men Who Have Sex With Men

Because DU MSM may engage in both high-risk drug use and sexual practices and may have multiple and different drug use behaviors and sex partners as well as networks, they not only constitute an important HIV risk group in and of themselves but also have the potential to serve

as a bridge for HIV to be transmitted to heterosexual IDUs and non-DU MSM. NIDA has recently issued a PA targeting this important population.

Adolescents

Among 13- to 19-year-olds, 7 percent of male AIDS cases and 15 percent of female AIDS cases were attributable to injection drug use exposure. These statistics, in combination with an increase in the use of marijuana and other drugs of choice among adolescents, highlight the importance of focusing HIV prevention on adolescents. In addition, data indicate a need for attention to understudied urban, disadvantaged, and ethnic minority adolescents, particularly homeless and runaway youth and young DU MSM.

NIDA is participating in the NIH-sponsored study of HIV-infected adolescents: Reaching for Excellence in Adolescent Care and Health (REACH). NIDA is also funding a study in Washington, D.C., on HIV infection and drug use/exposure in adolescents.

Native Americans

Native Americans represent an understudied population that requires more attention. Preliminary findings from a four-city multisite study of NIDA's Cooperative Agreement grantees revealed that out-of-treatment Native American drug users are at substantial risk for HIV infection. Almost all participants in the study were multiple-drug users. At one of the study sites, Native American women reported a higher mean frequency of drug use in the last 30 days than men for every drug report except for speedball. At another site, more women (64 percent) than men (41 percent) had a history of injection drug use. One site reported that, in the previous month, more women than men injected drugs, shared injection equipment, shared injection equipment without cleaning, and had IDU sex partners. At one of the four sites, more women (93 percent) than men (53 percent) reported having sex in the previous 30 days, with women being more likely to report multiple sex partners. Both men and women across all four sites reported significant risks related to their drug use and sexual behavior.

Recommendation 106 [Behavioral, Social Science, and Prevention Research ARP Report, p. 14, No. 8]

NIMH should expand its prevention research to additional populations including young and ethnic minority men (MSM), heterosexual minority and poor men, and young people in situations that make them vulnerable to HIV risk behavior.

Current Status

NIMH has sponsored a research program to develop specific interventions to change high-risk behaviors in emerging at-risk populations who frequently have multiple risk factors. These populations, such as young gay men, runaway and street youths, adolescents from socioeconomically disadvantaged backgrounds, prisoners, the homeless, and the mentally ill may be at substantially higher risk for HIV infection if they are practicing high-risk behaviors in a high-seroprevalence area. Behavioral interventions are the only effective prevention strategies to avert

further HIV infections. NIMH-funded investigators have adapted social cognitive models of behavior change and personal control to design interventions that combine imparting of information; developing skills in problem solving, sexual negotiation, and condom use; and identifying high-risk situations.

Future Actions

In order to target at-risk populations, NIMH has taken the lead in releasing several recent PAs. One PA is focused on "Brief Intervention to Prevent the Spread of HIV." This PA is particularly important because many at-risk populations will not take the initiative to participate in longer HIV prevention programs. Studies under this initiative are focused on reaching persons using brief but effective methods. Several studies have already been funded under this PA. One includes a "sex risk appraisal" that generates a personalized profile of risk behavior which can then be incorporated into the intervention so that it becomes individually tailored. Another intervention is focused on persons who repeatedly engage in high-risk sex behaviors and includes individualized uncovering of "self-justifications," that is, thoughts, attitudes, and beliefs that allow an individual to engage in high-risk behaviors despite knowing the risks.

In order to implement this recommendation, NIMH with OAR support has supplemented a group of ongoing grants on mental health services to focus on HIV prevention efforts among the seriously mentally ill and other emerging at-risk populations.

Research supported under this initiative will seek to understand sexual and injection drug use behavior and their determinants among the severely mentally ill and attempt to link these risk behaviors with seroincidence data. Such information will be used to develop and evaluate clinically appropriate risk-reduction strategies. Other studies will identify new methods for maintaining vigilance on the part of mental health care providers to identify persons at high risk. A major initiative is currently under way to develop preventive interventions that will be successful with patients who may have compromised mental abilities and who may be severely depressed.

Research will be initiated to develop education and risk-reduction interventions that target high-risk populations identified by behavioral epidemiological surveys. As part of this effort NIMH, along with other ICDs and HRSA, will continue to collaborate with the Department of Housing and Urban Development (HUD) on an initiative to provide technical assistance to communities in meeting the needs of homeless persons with multiple diagnoses. Through this initiative, NIMH will help in establishing, evaluating, and disseminating information on model programs to provide the integration of health care and other supportive services with housing assistance for homeless persons at risk or living with HIV infection.

NIMH, in collaboration with NICHD and other ICDs, will focus on women who have experienced at least one incident of sexual abuse in their lives before the age of 18. Victims of early abuse are also likely to be revictimized as adults, which contributes to low self-esteem and the inability to engage in self-protective behaviors, specifically those that can reduce the risk of HIV infection. This research initiative will support a special effort to examine the

interrelationship among early sexual abuse, domestic violence, and social stigma in impeding progress in AIDS prevention science.

Recommendation 107 [Behavioral, Social Science, and Prevention Research ARP Report, p. 15, No. 9]

The NIH should support more research that assesses the social, environmental, and cultural factors influencing changes in risk behaviors. Cross-national studies may be particularly useful for conducting research with units of analysis larger than the individual.

Current Status

NIH's support for studies of macro- and micro-level influences on risk behaviors is emphasized in the Behavioral and Social Science and the Natural History and Epidemiology sections of the FY 1998 NIH Plan for HIV-Related Research. Over a period of years, the ICDs have amassed a large body of research data related to the multiple factors that influence whether or not individuals and/or groups will engage in risk behaviors and the factors that account for changes in risk behaviors. Until recently, however, most epidemiological research focused on the individual's risk behaviors and aggregated them to the group level. Some NIH-sponsored research combined epidemiological and ethnographic research to help understand risk behaviors of vulnerable populations. More recent research efforts have begun to focus on the environment in which behaviors occur and the conditions and circumstances that influence high-risk behaviors or that encourage protective behaviors, as well as measure the effects of social and environmental factors. Across the ICDs, there is support for cross-national studies.

Future Actions

ICDs will publish PAs that will specifically address social context in relation to sexual behavior and HIV prevention. The NIH workshop on international prevention strategies mentioned in **Recommendation 104** also will address and help identify directions for further research on the social, environmental, and cultural factors influencing risk behavior**.** More attention will be focused on the structural factors that operate at the levels of the dyad, network, community, or larger geographic catchment areas.

In addition, please refer to the NIH responses to Recommendations 53 and 115.

Recommendation 108 [Behavioral, Social Science, and Prevention Research ARP Report, p. 15, No. 10]

In addition to studies of the sociocultural influences on risk behaviors, the NIH should encourage research that permits the identification of specific elements of successful interventions that may be related to behavior change (e.g., outreach, counseling, skills training, peer influences, or other components).

Current Status

NIH recognizes that investigators should be encouraged to evaluate different strategies and to document carefully what has proven successful and what has not. NIH-sponsored research has utilized many different strategies to effect behavior change. Outreach programs have been used with IDUs and persons on methadone maintenance and substance abuse treatment as a strategy to reduce HIV risk behavior. Motivational interviewing has been used with those struggling with alcohol abuse associated with high-risk HIV behavior. Counseling and serotesting have been used with persons who are contemplating behavior change. Skills training has been an important part of interventions based on social learning theories, while social diffusion theories have examined the effect of peers and shared norms on behavior change.

Future Actions

A dual strategy is needed to examine both behavior prediction and behavior change models to evaluate what components of interventions are successful in interrupting ingrained habits and which strategies are successful with different populations. Studies that examine the range and interaction of variables that influence behavior change are important, as are studies that examine the effect of different dose levels (number of sessions) and intensity (length of sessions) of interventions. Recent PAs that address these issues include NIMH's "Brief Interventions to Prevent the Spread of HIV" and the "AIDS Risk Reduction" addendum to NIDA's PA on behavioral therapies, which calls for research to identify specific components of interventions leading to behavior change within drug abuse treatment settings. In addition, NICHD sponsored a meeting in early 1997 that looked at middle childhood and developmental issues related to HIV prevention. NICHD also will publish a PA that will address many related concerns.

Recommendation 109 [Behavioral, Social Science, and Prevention Research ARP Report, p. 17, No. 11]

The NIH should encourage and support the use of quasi-experimental design alternatives (to the randomized controlled trial) that permit community-level trials to be undertaken in field-demonstration studies.

Please refer to the NIH response to Recommendation 75.

Recommendation 110 [Behavioral, Social Science, and Prevention Research ARP Report, p. 17, No. 12]

The NIH should encourage and support studies that assess the cost-effectiveness and cost-utility of behavior change interventions, including those that estimate or measure the number of potential HIV infections averted by an intervention.

Current Status

An increasing percentage of the national health and mental health care expenditures are being spent on the treatment of HIV infection and AIDS. The cost of treating HIV disease in 1993 was estimated to be $11.8 billion dollars. Policymakers, community planning groups, and other key health and mental health decision makers need to balance the costs and effectiveness of interventions when planning their HIV prevention and treatment programs. Well-designed economic evaluation studies can provide a database on the cost-effectiveness of HIV/AIDS prevention and treatment programs to inform these health policy decisions. NIH-supported research has begun to demonstrate that prevention strategies developed by behavioral and social scientists are cost-effective: each case of HIV infection that is avoided saves many dollars in medical treatment and lost human potential.

NIH concurs that better determining the cost-effectiveness of effective behavioral preventive interventions in this area is important, as reflected in the Behavioral and Social Science priorities articulated in the FY 1998 NIH Plan for HIV-Related Research.

Future Actions

NIDA is supporting new projects that develop and apply mathematical and economic models to evaluate HIV interventions. These efforts should assist in the further development of methodologies and applied policy analysis relevant to cost-effectiveness evaluations. Similarly, NIMH soon will release a PA on "Integrating Economic Evaluation into AIDS Prevention," which is expected to stimulate new AIDS prevention intervention applications that incorporate cost-effectiveness evaluation into the design of future prevention studies.

Recommendation 111 [Behavioral, Social Science, and Prevention Research ARP Report, p. 19, No. 13]

Basic research supported by NIMH, NICHD, and NIDA should be conducted within the following high-risk, understudied groups: gay men of color, young gay men, women who have sex with IDUs, bisexual men, and gay and bisexual drug users.

Recommendation 112 [Behavioral, Social Science, and Prevention Research ARP Report, p. 19, No. 14]

The following groups, currently with lower HIV prevalence, also merit special study because of their potential vulnerability: persons who are mentally ill, incarcerated persons, young adolescents (under 15 years of age), and later middle age and older adults. Research involving these groups should be supported by NIMH, NICHD, NIDA, and NIA, as appropriate.

Current Status

As articulated in the FY 1998 NIH Plan for HIV-Related Research, NIH is committed to expanding its basic behavioral and social science efforts that are directed to developing models of behavior and behavior change that integrate biological, psychological, and social factors associated with the acquisition, change, and maintenance of HIV-related behaviors in a broader

range of populations. NIDA, for example, has recently issued a PA for the purpose of supporting epidemiological and HIV prevention research on drug use, sexual-risk behaviors, and HIV in an especially high-risk group: men who use drugs and have sex with men. This multifaceted effort is focusing on basic principles for determinants, mediators, and reinforcers of behavior and will attempt to understand fundamental mechanisms of behavior developmentally and over the life-course, particularly human information processing and self-protective behaviors.

Future Actions

NIH will continue to expand efforts to examine specific risk profiles of subgroups of understudied populations. Basic research of this kind will help to develop behavioral and biomedical interventions that may be applied to prevention, diagnosis, treatment, and rehabilitation in HIV/AIDS, mental illness, and substance abuse. The data from NICHD-supported Add-HEALTH interviews with young people ages 12 to 18 also will become available to investigators and will be a unique resource for basic research on these issues; NICHD also will publish a broad PA that will encourage researchers to explore HIV-related prevention issues in these population groups. In addition, NIH will continue to support research that identifies the factors that affect recruitment, retention, and treatment adherence in clinical trials, as well as support other prevention research of understudied groups.

Recommendation 113 [Behavioral, Social Science, and Prevention Research ARP Report, p. 20, No. 15]

> *NIDA, NIMH, NICHD, and NIAAA should support theory-building studies that are specifically developed in the context of HIV prevention research, in contrast to studies that simply apply or adapt theories from other domains.*

Recommendation 114 [Behavioral, Social Science, and Prevention Research ARP Report, p. 20, No 16]

> *NIDA, NIMH, NIAAA, and NICHD should support qualitative/descriptive/ethnographic studies of the subjective difficulties individuals experience in their attempts to practice safer sex or safer drug-using behavior, and of situations/contexts that are subjectively experienced as difficult for enacting and maintaining safer behavior.*

Current Status

NIH supports theory-based research studies related to HIV prevention. Historically, much of the early research was informed by a limited set of behavioral science theories relating to risk behavior and behavior change that were developed in non-AIDS contexts and were primarily focused on the individual. More recently, however, the ICDs have begun to rely on a variety of theoretical perspectives, from a broader range of behavioral and social sciences, including those that are useful in explaining and/or predicting individual behavior and behavior change, those focused at changing dyadic and/or larger groups of networks, and those focused on community-level change. Nevertheless, there is still a need to more clearly link theory and elements of theoretical models to the design of interventions and to the measurement of outcomes that specifically relate to HIV infection and AIDS (e.g., theories of sexuality, gender, stigma, community mobilization).

In 1995, the OAR sponsored an IOM workshop on "Assessing the Social and Behavioral Science Base for HIV/AIDS Prevention and Intervention," which focused on theory, models, and observational approaches that may be useful to the design of HIV prevention initiatives. NIDA recently sponsored a meeting of anthropologists to discuss the contributions of their theoretical work to HIV prevention and intervention among IDUs. In 1992, NIMH sponsored a meeting of five major theorists who identified eight variables that are crucial for effective behavior change interventions.

Future Actions

With the formation of the OARAC PSWG and the development of the FY 1999 NIH Plan for HIV-Related Research, OAR and the ICDs will continue to encourage the research community to address theoretical issues related to HIV prevention. NICHD will issue a PA inviting investigators to use a variety of approaches to HIV-related sexual behavior research, drawing upon a number of social science domains, and building upon its current support of ethnographic, sociological, and network studies.

Recommendation 115 [Behavioral, Social Science, and Prevention Research ARP Report, p. 20, No. 17]

> *All ICDs with a behavioral and social science portfolio should support basic research that involves units of analyses other than the individual.*

Current Status

NIH agrees that a critical strategy for addressing the AIDS epidemic that builds upon the successes of studying the individual to understand health-risk behaviors is to employ larger units of analysis such as couples and sexual networks in the context of neighborhood and community settings. NIH-supported researchers, particularly from the behavioral and social sciences, have highlighted the importance of macro-level units of analysis to gain a different perspective on the etiology, prevention, and treatment of HIV-related risk behaviors (unprotected sexual intercourse, the use of contaminated injection drug equipment, etc.). NICHD and NIMH support research with couples and families as units of analysis; NIDA supports research with drug using and sexual networks as units of analysis; and NICHD and NIAID, among others, have supported community-level treatment and intervention studies.

Future Actions

ICDs that support behavioral and social science research on AIDS will further develop research approaches that employ units of analysis larger than the individual to gain a better understanding of how to study health behavior in the aggregate and factor in norms associated with the affected AIDS-risk target population. ICD-supported programs will continue to promote research to develop theories that take into account the role of couples, sexual networks, and the environments in which health-risk behaviors occur to determine how these larger units of analysis operate and

how their behavioral dynamics either increase the probability of risk for exposure to HIV or may be used to prevent exposure.

In addition, please refer to the NIH responses to Recommendations 53 and 107.

Recommendation 116 [Behavioral, Social Science, and Prevention Research ARP Report, p. 21, No. 18]

NICHD and NIMH, individually or collaboratively, should support basic research on those individual differences in human sexuality—cultural, cognitive, affective, and neurophysiological—that impact the sexual transmission of HIV. For example, attention should be paid to the relevance of the relationship (i.e., intimate/romantic, involving strong emotional bonds) on sexual risk behavior, and also to neurobiological mechanisms that might interfere with sexual self-regulation in the context of safer sex practices.

Current Status

Several of ICDs, principally NICHD and NIMH, conduct basic research on human sexuality and its determinants at multiple levels of scientific analysis. Questions of human sexuality within a developmental framework are addressed by NICHD's Add-HEALTH study, a national longitudinal study, which is assessing the development and maintenance of romantic and sexual relationships in adolescents, and studies of the sexual identities of young women. Both NICHD and NIMH sponsor basic research on the hormonal and neurobiological underpinnings of reproductive behaviors. In addition, both Institutes support research on the developmental psychobiological aspects of puberty onset and sexual initiation (debut). NICHD also supports research related to skill building in various populations regarding the use of condoms both as a family planning approach and a way to reduce risk of exposure to STDs. Furthermore, NICHD supports research on social networks related to sexual behavior in adults and teens and studies of cultural and social determinants of individuals' sexual behavior. NIMH has supported multiple studies in basic research that examine determinants of HIV-related risk behaviors in adolescents and women. There also is a vigorous research program on information processing and decision-making at different levels of emotional arousal that affect behavior toward safer sexual behavior.

Future Actions

NIH will encourage an expansion of high-disciplinary research at the NICHD and NIMH on human sexuality life-span issues (children, adolescents, and adults) to design more effective AIDS prevention and intervention programs. This research will focus on the biobehavioral mechanisms that underpin cognitive, emotional, and neuropsychological processes related to sexual behaviors that increase an individuals chances of being exposed to HIV. Additional basic research will be supported by the ICDs to understand how biobehavioral mechanisms involved in affective bonds increase an individual's chances of engaging in risky sexual behaviors. NICHD and NIMH will expand research to determine what neurobiological mechanisms may place some individuals at

higher risk for engaging in risky sexual practices and, thereby, increase the risk of exposure to HIV infection.

NICHD also will publish a PA that will include, among other items, an emphasis on studies of how relationship characteristics and dynamics in their cultural contexts affect partner selection and HIV-related sexual behavior.

Recommendation 117 [Behavioral, Social Science, and Prevention Research ARP Report, p. 22, No. 19]

> *NIAAA, NIMH, and NIDA should support studies that examine in detail the use and abuse of alcohol/drugs within the context of sexual encounters and the direct effects of these intoxicants on sexual self-regulatory mechanisms.*

Current Status

NIAAA, NIDA, and NIMH support studies that examine in detail the use of alcohol and other substances and its direct and indirect effects on sexual risk-taking behaviors. Current research employs primarily retrospective self-report methods through the use of questionnaires and diaries and, to a lesser extent, case studies and qualitative ethnographic methods.

Investigator-initiated research is encouraged through a range of PAs. NIDA and NIAAA currently support research related to the impact of substance use on sexual transmission of HIV in at-risk populations. Announcements include PA-96-074 (NIDA) "Drug Use, Sexual Behaviors and HIV in Men," PA-95-054 (NIDA) "Strategies to Reduce HIV Sexual Practices in Drug Users," and PA-91-75 (NIAAA) "Research on the Relationships Between Alcohol Use and Sexual Behaviors Associated With HIV Transmission."

Future Actions

NIH will encourage more experimental research that examines changes in alcohol/drug use and cognitive expectancies within laboratory settings, including the effects of behavioral and pharmacological interventions, and that examines the effects of substance use on disinhibition and on outcomes of specific sexual encounters.

Recommendation 118 [Behavioral, Social Science, and Prevention Research ARP Report, p. 22, No. 20]

> *NIDA and NIAAA should devote special attention to research on the impact of drug and alcohol use on the sexual transmission of HIV among gay men and on how initiation into alcohol and/or drug use might have an impact on sexual risk taking among adolescents.*

Current Status

NIAAA and NIDA agree that research on the impact of substance use on sexual transmission of HIV is an important area of research, as the co-occurrence of alcohol and substance use is an excellent predictor of both sexual risk patterns and increased seroincidence. NIAAA and NIDA support basic behavioral research on gay men who have alcohol and/or drug abuse problems and encourage the development and testing of individual and community-based interventions to address these problems. Interventions among gay substance users has shown substantial reductions in HIV risk behaviors. Interventions within the context of alcohol treatment units also have been effective in reducing HIV risk.

At present, NIAAA encourages investigator-initiated research to promote research in interventions within the context of substance use. NIAAA has issued an RFA, "Development and Testing of HIV Preventive Interventions Among Alcohol Users," to encourage research among gay men. Investigator-initiated research also is encouraged through a range of PAs. NIDA and NIAAA currently support research related to the impact of substance use on sexual transmission of HIV in at-risk populations. Announcements include PA-96-074 (NIDA) "Drug Use, Sexual Behaviors and HIV in Men," PA95-054 (NIDA) "Strategies to Reduce HIV Sexual Practices," and PA-91-75 (NIAAA) "Research on the Relationships Between Alcohol Use and Sexual Behaviors Associated With HIV Transmission."

Future Actions

NIAAA and NIDA will continue to support a wide range of both theoretical and applied studies on adolescent substance users. Although research on gay adolescents currently is limited primarily to studies of homeless and runaway youth—as these individuals may be particularly susceptible to alcohol and/or drug use and sexual abuse—additional research on gay adolescents in a wider range of settings will be encouraged.

Recommendation 119 [Behavioral, Social Science, and Prevention Research ARP Report, p. 22, No. 21]

> *NIDA should expand its support for studies on the exchange of drugs for sex and sex for drugs to include substances other than crack cocaine.*

Current Status and Future Actions

NIDA agrees with the importance of the link between sexual risk behaviors and drug use and will continue to support research in this area.

NIDA was instrumental in the identification and characterization of the "sex for crack" phenomenon and is continuing ethnographic and epidemiological research critical to these types of findings.

NIDA is supporting a new program initiative to address the increasing rates of HIV seroincidence in a diverse, vulnerable, and understudied population: men who use injection and noninjection

drugs and who have sex with men. A PA entitled "Drug Use, Sexual Behaviors, and HIV in Men" (PA-96-074) has just been released to encourage new epidemiological and HIV prevention research focused on DU MSMs. Methamphetamine is a popular drug of choice among DU MSMs, particularly in the western part of the United States. Used intranasally, by inhalation, and by injection, it is becoming a major problem among gay and bisexual men because of its addictive properties and strong association with high-risk sexual behaviors and HIV.

NIDA also is sponsoring a 2-year project that is an ethnographic (exploratory) study of gay and bisexual methamphetamine needle users in the Seattle area. Little is known about the multiple HIV and drug-related risk behaviors of MSMs who inject methamphetamine, yet drug use indicators for methamphetamine-related problems in this dual-risk group have steadily increased. Results from this project are expected to provide insights into the risk behaviors of methamphetamine-using MSMs and to serve as a basis for developing a high-phased HIV prevention and intervention project.

Recommendation 120 [Behavioral, Social Science, and Prevention Research ARP Report, p. 23, No. 22]

> *NICHD and NIMH should support research on the sexual transitions of young adolescents including research on the initiation into homosexual and/or heterosexual activity and the related "coming out" or "experimenting" processes. In addition, studies are needed that investigate the biological and social precursors of these transitions, particularly when they are not voluntary.*

Current Status

NIH recognizes that there is a special need to prevent HIV-related risk behaviors during periods of transition for adolescents and adults. NICHD, for example, has supported studies of the sexual transitions of young adolescents and the biological and social precursors of these transitions since the early 1970s and has funded a variety of demographic studies that link marital status to HIV-related risky sexual behavior.

NIMH-supported studies have documented that adolescents, particularly pre- and early adolescents, whose parents monitor their activities tend to delay the initiation of sexual activity. Interventions that provide AIDS education and parenting skills are a way to maintain abstinence in young people. Also, programs have demonstrated that explicit education about HIV infection and how to practice safer sex also contribute to a delay in becoming sexually active.

Future Actions

NIH may consider developing a PA on research focused on adolescents. Resources permitting, the National Institute on Aging (NIA) will expand its efforts to understand and target risk behaviors among older persons, especially those who experience significant transitions in their relationship status.

Recommendation 121 [Behavioral, Social Science, and Prevention Research ARP Report, p. 23, No. 23]

NIDA and NICHD should support research on the progression of substance use over time. Recent findings suggest that first-time initiates and younger drug users are turning to forms of noninjection drug use in part to avoid HIV transmission. Studies are needed that investigate and map possible progressions into riskier forms of drug use in relation to HIV transmission.

Current Status

NIH agrees that more research must focus on changing behavior and patterns of drug users and assessing the determinants of these changes, with particular attention to age at initiation of drug injection practices. Currently, NIDA is supporting several epidemiological and ethnographic studies focusing on the transition from noninjection to injection-related behaviors and HIV consequences.

Future Actions

NIDA is developing an initiative to study issues related to drug abuse and HIV/AIDS and, specifically, the initiation of injection behavior. NIDA will work with NICHD to identify further avenues for exploring this issue among younger persons.

Recommendation 122 [Behavioral, Social Science, and Prevention Research ARP Report, p. 23, No. 24]

NIA should collaborate with NIMH and NICHD to support more descriptive research about the HIV risk behavior of individuals who are in life stages and/or transitions that increase risk. These groups include pregnant unmarried women, recently divorced men and women, and individuals over the age of 50.

Please refer to the NIH response to Recommendation 120.

Recommendation 123 [Behavioral, Social Science, and Prevention Research ARP Report, p. 24, No. 25]

NIMH, NICHD, and NIDA should support research on "resilient" individuals who, in the face of difficult circumstances, are successful in adopting and maintaining safe sex and/or drug-using behavior.

Current Status

NIH agrees with the Panel that it is extremely important to identify those factors associated with resilience and successful behavior change that operate despite overwhelming life circumstances. Research has demonstrated that bad moods increase preference for risky behaviors and that

depression contributes to less effective control of behavior which places these individuals at increased risk for HIV infection.

NIH has supported large national population-based behavioral and epidemiological studies in order to identify the determinants and distribution of high-risk HIV-related behaviors. Studies of knowledge, attitudes, and behavior of specific at-risk populations also have been undertaken. The data from these two research strategies have been used to develop behavioral AIDS prevention programs. Data from NICHD's population-based study, Add-HEALTH, may help define resilience. Findings from an NIMH-supported Phase III multisite study, with both biologic and self-report outcomes, that will be unblinded in May 1997, will permit an assessment of the characteristics of the resilient individuals for whom specific parts of the intervention were successful during stressful life situations or when opportunities existed to engage in risk-taking behaviors.

NIDA also is supporting a 23-site epidemiological and prevention research study of IDUs and non-IDUs at risk for acquiring and transmitting HIV infection. This ongoing study has provided and will continue to provide data on the efficacy of high-component intervention strategies to reduce HIV risks—both sexual and drug-use-related—and prevent HIV infection. Additional data from this study will permit researchers to determine the characteristics of at-risk individuals who have reduced their risk, maintained their risk behaviors, or increased their risk over time.

Future Actions

Issues of behavioral organization, developmental malleability, and resilience still need to be better understood. To this end, NIH will expand research that characterizes how behavioral risk factors in general combine to determine the degree to which a person is at risk for HIV infection. Special attention will be paid to the relationship between HIV risk factors and how individuals evaluate their level of risk and self-label (e.g., as gay, bisexual, heterosexual). This research will have important implications for the validity and reliability of self-report measures.

Recommendation 124 [Behavioral, Social Science, and Prevention Research ARP Report, p. 24, No. 26]

> *NIMH and NICHD should support research on the relationship between "sexual addiction" and HIV risk taking.*

Current Status

NIH concurs with the spirit of the Panel's recommendation that NIMH and NICHD should support research on the relationship between frequent and compulsive sexual behavior and HIV risk taking, although the term "sexual addiction" is problematic. In collaboration with NIDA and NINR, NIMH developed a PA, "Preventing Relapse to High-Risk HIV Behaviors," which is soliciting grants on maintaining behavior change. The major objective is to identify effective ways to prevent relapse to behaviors—including sexual behaviors—that place persons at high risk for HIV infection.

Future Actions

NIH will expand its research program directed to developing models of behavior and behavior change that integrates biological, psychological, and social factors associated with the acquisition, change, and maintenance of HIV-related risk behaviors. The focus on understanding decision-making processes will be expanded to examine the processes associated with the adoption of protective behaviors and the relapse to high-risk behaviors and the resistance to change despite having knowledge about HIV/AIDS and its transmission.

Other research areas targeted for increased efforts include research on (1) the factors that differentiate persons who relapse from those who maintain low-risk behaviors; (2) the effect of alcohol and drug use on judgment, decision making, and perception of risk associated with relapse to high-risk behaviors; (3) the way in which low self-efficacy and a sense of helplessness may contribute to relapse; (4) the means by which coping with relapse episodes can stimulate recovery to low-risk behaviors; and (5) the social pressures associated with relapse and how changing social norms can ensure maintenance of safer sexual and drug-use behaviors.

Recommendation 125 [Behavioral, Social Science, and Prevention Research ARP Report, p. 24, No. 27]

Intervention studies funded by NIH should analyze systematically the reasons, variables, and/or characteristics that may explain individuals' susceptibility (or resistance) to HIV interventions.

Please refer to the NIH response to Recommendation 123.

Recommendation 126 [Behavioral, Social Science, and Prevention Research ARP Report, p. 25, No. 28]

NIMH, NICHD, and NIDA should support longitudinal studies of individuals' and/or groups' ability to maintain safe behavior over time and of those factors that may inhibit or promote relapse to unsafe practices.

Please refer to the NIH response to Recommendation 124.

Recommendation 127 [Behavioral, Social Science, and Prevention Research ARP Report, p. 26, No. 29]

NIMH and NIDA should support (in some cases in collaboration with other ICDs) research to prevent transmission by HIV-infected persons, including studies to determine the prevalence and determinants of risk behavior among HIV-infected persons and studies to develop and test interventions to reduce behaviors that place others at risk.

Current Status

NIH agrees that it is important to enhance attention to prevention strategies focused on the behavior of HIV-infected persons, as reflected in the Behavioral and Social Science priorities in the FY 1998 NIH Plan for HIV-Related Research. For example, NIDA is supporting research to investigate factors associated with HIV-related risk behaviors among methadone maintenance patients, including both HIV-infected and uninfected drug users. The potentially beneficial role of pharmacotherapy in altering HIV-related risk behaviors in addicts is under investigation. NIDA also has recently funded the development and testing of an intensive behavioral therapy to reduce HIV-related risk behaviors among HIV-infected drug users. NIMH has been providing technical assistance to investigators who are planning a large collaborative effort to test an effective AIDS intervention with HIV-infected persons to prevent the further spread of HIV.

Future Actions

The OAR Coordinating Committee on Behavioral and Social Science Research will address this area during its development of the FY 1999 Plan and will seek the advice of the OARAC PSWG on additional avenues for expanding research.

Recommendation 128 [Behavioral, Social Science, and Prevention Research ARP Report, p. 28, No. 30]

> *NIMH, NIDA, NICHD, NIA, and NINR (as relevant) should increase intervention research directed toward improving coping and quality of life among HIV-infected persons from all populations, across the full time-course of HIV illness.*

Current Status

An expanded NIH research program is directed at extending the asymptomatic stage of HIV infection and improving the quality of life of individuals infected with the virus. For example, NIMH is supporting research, currently under assessment, that suggests that personal resilience and effective behavioral and cognitive strategies can reduce the stress that often accompanies HIV infection and have palliative effect on disease course. NIDA is supporting the development of Risk Reduction Therapy, a comprehensive drug abuse treatment intervention for HIV-infected persons that strives to increase health-promoting attitudes and behaviors, including stress management, management of depression, coping strategies, and improved daily-living skills.

Future Actions

Effective prevention strategies require the cooperation and support of HIV-infected individuals and their integration into adaptive social-support networks—factors that are adversely affected by psychological distress and poor mental health functioning. Research will be supported to determine new ways to strengthen social ties of HIV-infected people and to encourage the participation of informal caregivers.

NIMH intends to support a multisite study that will focus on behavioral prevention efforts and health promotion activities with HIV-infected individuals to slow disease progression and enhance quality of life. Two cohort studies of long-term survivors also are being supported to identify any psychosocial or biobehavioral correlates that may suggest intervention strategies to slow disease progression.

NIDA will encourage all treatment research investigators targeting HIV-infected patients to include strategies that address quality of life. Under its research program to improve the medical care of HIV-infected persons, NIDA is undertaking an initiative focused on identifying, treating, and preventing clinical disease that diminishes drug abusers' quality of life. One initiative will identify medical/psychiatric/health issues for treatment-resistant active drug users, with the goal of developing more effective interventions for these hard-to-reach users. Another initiative will focus on treating comorbid psychiatric disorders in HIV-infected drug users.

Recommendation 129 [Behavioral, Social Science, and Prevention Research ARP Report, p. 29, No. 31]

NIMH and NIDA should expand research describing the impact of HIV disease on formal and informal caregivers, as well as on family members, and they should increase intervention research designed to address the needs of these groups.

Current Status

NIH acknowledges the importance of expanding research on the impact of HIV disease on caregivers. NIMH and NIDA are supporting the testing of interventions developed to ensure the physical and mental health of people with AIDS and their caregivers. Studies are examining specific problems and effective coping strategies adopted by HIV-infected persons and their caregivers across the stages of HIV disease.

NIH will continue to support research on the impact of caregiving on the families and friendship networks of HIV-infected individuals and to evaluate the effectiveness and cost utility of different models of health care. The ICDs are collaborating with HRSA and AHCPR on the HCSUS. This large, national probability sample of health care by services cost and utilization by persons with HIV infection and AIDS will gather information on formal and informal caregivers as well as patients that will serve as the basis for developing intervention research on quality of care and cost-utilization. Furthermore, this study will document the health care service needs and utilization of mentally ill persons with HIV infection and AIDS. These data will form the basis for research on effective treatments of the severely mentally ill with AIDS.

Future Actions

NIH will utilize the research findings of the HCSUS project to guide the direction of future research.

Recommendation 130 [Behavioral, Social Science, and Prevention Research ARP Report, p. 29, No. 32]

NIMH and NIDA should initiate research on the impact of stigmatization on HIV-infected persons, including the influence of stigmatization on coping with HIV disease, decisions regarding treatment, and quality of life.

Current Status

NIH is committed to examining all forms of social discrimination that have an impact on the AIDS epidemic. NIMH has been supporting a national public opinion survey that has identified the prevalence of stigmatizing attitudes and beliefs toward HIV infection and AIDS among the U.S. adult population (e.g., in ethnic and racial groups and various age groups) and shown how that prevalence of stigma has changed over time. There are several other studies examining the role of educational materials and the media in perpetuating social discrimination.

The social construction of HIV/AIDS in the United States has made it one of the most stigmatizing medical conditions and has led to a secondary epidemic of fear, prejudice, and discrimination against people with AIDS and HIV-infected individuals. This epidemic of fear contributes to misinformation about the risks of HIV infection, increases prejudicial attitudes about those who are seropositive, and begins a cycle of isolation and depression among the affected population.

NIDA recognizes that HIV-infected drug abusers face dual stigma related to their drug abuse and HIV infection; data suggest that HIV-infected drug abusers receive fewer medical services for their HIV disease than other HIV-infected populations. NIDA is undertaking an initiative to improve delivery of medical care to HIV-infected drug users, and this initiative will focus on stigmatization as an important factor in treatment seeking, access to treatment, and compliance.

Future Actions

NIMH and NIDA will encourage the development of interventions designed to eliminate HIV-related social discrimination and its consequences that are based on the findings from these current studies.

Recommendation 131 [Behavioral, Social Science, and Prevention Research ARP Report, p. 31, No. 33]

Conduct coordinated and collaborative research on the pathobiology of nervous system HIV infection and nervous system injury underlying the AIDS dementia complex, peripheral neuropathies, and other CNS and PNS complications of HIV and AIDS. These studies should be multidisciplinary efforts that focus on the cellular and molecular basis of viral latency, gene expression and replication in neural tissue, and the regional, cellular, neurochemical, and molecular basis of neural dysfunction. Research strategies should involve direct studies of human infection, animal models (including a spectrum of

lentivirus models), and cell culture studies. NINDS, NIMH, NIDA, NIAID, and NICHD should work together to ensure that these studies benefit from broad expertise, state-of-the-art science, and the efficient utilization of resources.

Recommendation 132 [Behavioral, Social Science, and Prevention Research ARP Report, p. 31, No. 34]

Expand research on the treatment of the neurological and psychiatric sequelae of HIV infection. The scope of this research should range from cell culture and animal models to human clinical trials. These efforts should also involve cooperation and coordination among NINDS, NIMH, NIAID, NICHD, and other ICDs as appropriate.

Current Status

NIH supports a vigorous program of research on the AIDS dementia complex, peripheral neuropathies, and other CNS and peripheral nervous system (PNS) complications of HIV infection. Two of the NIMH AIDS Research Centers specifically focus on the cellular and molecular basis of HIV-related nervous system disorders and the neuropsychiatric sequelae of HIV infection. NIDA's initiative to improve delivery of medical care to HIV-infected drug users also addresses the treatment of neurological and psychiatric sequelae of HIV infection.

In addition, NIAID evaluates potential therapies for primary HIV CNS involvement through the ACTG Neurology Committee. This committee collaborates with the NINDS, which established the NARC in an effort to improve coordination of clinical research on HIV-associated neurological complications. One component of the NARC clinical trial deals with therapies for AIDS dementia. Patients are followed using standard neuropsychological testing.

Future Actions

NIH is establishing a cross-Institute neuro-AIDS interest group. This group should facilitate and clarify the types of investigations that represent ongoing interests versus healthy overlap. NINDS will continue to use grant or contract mechanisms in supporting research as well as actively seek the financial participation of other ICDs in joint funding of large grants, centers, and program projects. In addition, NIH will explore the use of joint PAs among NINDS, NIMH, NIAID, NICHD, NIDA, and other ICDs that share a common interest in supporting research on treatment of neuro-AIDS.

Recommendation 133 [Behavioral, Social Science, and Prevention Research ARP Report, p. 32, No. 35]

Initiate research to investigate the determinants and barriers to timely HIV testing and entrance into care by HIV-infected persons from all vulnerable populations.

Recommendation 134 [Behavioral, Social Science, and Prevention Research ARP Report, p. 32, No. 36]

Develop and test intervention strategies to increase the early identification, timely entrance into care, and effective management of disease in HIV-infected persons from all vulnerable populations.

Current Status

NIH recognizes the importance of developing strategies to increase the early identification and entrance into care of persons at the earliest stages of HIV infection. One current NIH initiative addressing this issue is NIAID's domestic HIVNET, whose sites are conducting a feasibility study (HIV Early Detection Study) of home specimen collection at monthly intervals to identify newly acquired HIV infection.

The Adolescent Medicine HIV/AIDS Research Network, supported by a number of ICDs, is studying the issue of how adolescents from vulnerable populations decide to access HIV testing and how they utilize the information gained from test results to influence their health-care-seeking behavior and their compliance with therapeutic and preventive strategies.

Future Actions

NIH will explore the possibility of linking studies that investigate behavioral strategies for enhancing HIV testing and early identification and recruitment into care of HIV-infected persons with current biomedical studies of primary and acute infection.

Recommendation 135 [Behavioral, Social Science, and Prevention Research ARP Report, p. 33, No. 37]

NIMH, NIAID, and where appropriate, NIDA should cooperate to support research to determine the social, psychological, environmental, and medical factors associated with recruitment, adherence, and retention in clinical trials and care for persons with HIV/AIDS.

Recommendation 136 [Behavioral, Social Science, and Prevention Research ARP Report, p. 34, No. 38]

NIMH, NIAID, and where appropriate, NIDA should cooperate to support research to develop and test intervention strategies to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV-infected persons from all vulnerable populations.

Current Status

NIH regards recruitment, retention, and adherence as critical factors to both HIV treatment and prevention studies. NIMH, NIAID, NIDA, and NIAAA support numerous studies on the behavioral and psychosocial factors and on interventions to enhance them. While the ICDs have not developed extensive collaborations in this area of research, they have worked together in

establishing a priority in the NIH Plan for HIV-Related Research on developing interventions to enhance recruitment, retention, and adherence in HIV prevention research studies.

The NIAID ACTG and CPCRA have included studies of enrollee adherence in a number of protocols. One study led to the development and validation of HIV-specific and general health-related quality-of-life scales. These scales are now used as endpoints in other clinical trials because the clinical endpoints (of enrollee demise or disease progression) may not reflect factors important to patients such as level of functioning and side effects. Thus, treatment decisions can be tailored to patient preferences related to quality-of-life measures.

NIMH is supporting a multisite trial that has developed a detailed protocol and guidelines that articulate principles for recruitment, retention, and adherence of hard-to-reach HIV at-risk populations. NIMH is planning to publish these guidelines so that they may be disseminated to investigators who are planning AIDS prevention studies. The NIMH AIDS Prevention Consortium and other investigators also have focused on these methodological issues in the conduct of effective trials.

NIAID's HIVNET vaccine preparedness study is examining factors associated with recruitment and retention of subjects into prevention studies. Included is a study of the acceptability of different methods of providing educational information about AIDS vaccines. Subgroup analysis will be undertaken to determine factors that are unique for women, minorities, gay men, and IDUs.

NIAID and NIDA are collaborating to support a drug use working group in the WITS study to evaluate the impact of drug use on pregnancy outcomes, the influence of drug use on acceptance and adherence to PHS guidelines regarding perinatal use of AZT to reduce the risk of vertical transmission, and the impact of maternal drug use on the risk of perinatal transmission.

NIAID and CDC are collaborating on a qualitative study to identify factors associated with acceptance of AIDS vaccines by communities. Focus groups, interviews, and multimedia approaches are being used.

Future Actions

The following efforts are under way to increase interagency collaborations:

- NIAAA and NIAID have signed an interagency agreement to support analysis of the influence of alcohol use on HIV-related risk behaviors among subjects in the HIVNET prevention studies.

- NIAID- and NIMH-funded investigators are collaborating on a study to enhance the process of informed consent for participation of at-risk women in AIDS vaccine efficacy trials.

- NIDA is undertaking an initiative to stimulate research on the delivery of medical care to "treatment resistant" HIV-infected drug users. One aspect of this initiative will address

how to improve HIV therapy adherence and, indirectly, study adherence. For this work, NIDA is collaborating with HRSA through its Special Projects of National Significance Program to develop research plans for improving HIV therapy compliance and chronic care compliance in drug-using HIV-infected individuals.

Recommendation 137 [Behavioral, Social Science, and Prevention Research ARP Report, p. 36, No. 39]

Because methodological issues transcend specific ICDs, the OAR should establish committees of experts and support them on an ongoing basis to develop standards regarding the use of various design options and guidelines for the appropriate use of various outcome measures (e.g., self-reported behavior, incident STDs, or HIV).

Current Status

There is significant interest among the HIV experts in the ICDs to engage in discussions on methodological issues in HIV-related behavioral and social science research. ICDs already have sponsored technical meetings on various methodologies, including advanced social network analysis, the evaluation of interventions (including cost-effectiveness analysis), the measurement of demographic behaviors, and the use of biologic outcomes in efficacy trials of behavioral interventions. In addition, two major conferences occurred in FY 1997: one, sponsored by the NIH Office of Behavioral and Social Sciences Research, addressed issues in self-report methodologies; the other, sponsored by NIMH and the NIH Office of Medical Applications Research, addressed outcomes of behavioral interventions which could provide guidelines that could best be disseminated. In addition, a series of activities supported by NIH and CDC are attempting to devise performance principles and standards for assessing the effectiveness of HIV prevention interventions to assist in the transfer of research to community-based services.

Future Actions

Rather than create additional committees to address methodological issues, OAR will continue to support the activities of ICDs and other NIH offices in this area and will use its Coordinating Committees to promote the activities.

Recommendation 138 [Behavioral, Social Science, and Prevention Research ARP Report, p. 36, No. 40]

The ICDs should develop programs, using the RFA or contract process, to stimulate methodological research on the issues identified in this report or through the ongoing process of scientific priority setting under the direction of the OAR.

Current Status

NIH recognizes that increased attention should be focused on methodological research, that using a variety of mechanisms would help to establish a program of research related to methodology,

and that OAR can contribute to establishing such a research program through its setting of scientific priorities. Indeed, methodological research is identified as a priority area in the FY 1998 NIH Plan for HIV-Related Research. In response to this priority area, some ICDs may amend PAs to encourage researchers to undertake appropriate methodological research.

ICDs often use RFAs and contracts to support methodological research. For example, NIAAA strongly supports methodological research in the study of mediators and moderators of HIV-related risk behaviors and biological outcomes related to substance use and abuse. Several contracts, R01s, and a Memorandum of Understanding have been funded to extend methodological research on global, situational, and event-based analysis of alcohol use and risk-taking behavior. Of particular importance is the study of situations in which HIV-related risk behavior is enacted under the influence of alcohol and/or drugs. Other ICDs, through their ongoing multisite collaborative studies, support methodological research (e.g., the NIMH multisite prevention trial and the NIDA cooperative agreement program).

Future Actions

OAR and its Coordinating Committees will work with the ICDs to identify the optimal strategies for promoting methodological research.

In addition, please refer to the NIH response to Recommendation 137.

II. SPECIAL ISSUES IN AIDS RESEARCH FUNDING

Recommendation 139 [Behavioral, Social Science, and Prevention Research ARP Report, p. 39, No. 41]

Given the crucial importance of training for the research enterprise, the OAR should appoint a separate coordinating committee to review and make recommendations on NIH AIDS-related activities listed under "Training and Infrastructure" in the NIH Plan for HIV-Related Research.

Please refer to the NIH response to Recommendation 9.

Recommendation 140 [Behavioral, Social Science, and Prevention Research ARP Report, p. 39, No. 42]

The OAR should develop a coordinated plan for HIV/AIDS-specific behavioral science research training that takes advantage of a wider range of NIH training mechanisms (such as the K awards, supplements, and predoctoral research opportunities). The plan should include strategies for the systematic outcome evaluation of training awards.

Current Status

NIH concurs with the Panel on the need to provide both domestic and international training in behavioral research on HIV, as noted in the FY 1998 NIH Plan for HIV-Related Research. NIH offers a number of research training mechanisms ranging from individual to institutional awards—both domestic and international—including F31, T32s focused on AIDS and AIDS supplements in other research areas, various K awards, P50s, and supplements for underrepresented minority researchers. Among the programs that could serve as vehicles to further expand behavioral science research training are FIC's AITRP and NIMH and NIDA's B/START programs.

However, in order to more rapidly and effectively address critical HIV-related behavioral issues, it is essential that additional targeted efforts be employed.

Future Actions

OAR will identify a contact person for training, infrastructure, and capacity building to address these and other training issues (such as training for minority researchers). This individual will coordinate these issues, which will be incorporated into the annual NIH Plan for HIV-Related Research. In order to be effective in this capacity, this contact person will seek ICD input for making recommendations on useful steps that can be taken to better address training, infrastructure, and capacity building needs.

In addition, please refer to the NIH responses to Recommendations 9–13.

Recommendation 141 [Behavioral, Social Science, and Prevention Research ARP Report, p. 40. No. 43]

The NIH should increase funding and programs for AIDS-related research training explicitly tailored and targeted to ethnic minority individuals, primarily at the postdoctoral level. These programs should involve collaborative mentoring activities in research projects defined by the minority scientists, rather than simply providing supplements to existing grants. Programs should include intense and long-term mentoring and support in the NIH grant application process, and they should be evaluated in relation to a measurable increase in the number of minority NIH-funded principal investigators at the NIH.

Please refer to the NIH response to Recommendation 13.

Recommendation 142 [Behavioral, Social Science, and Prevention Research ARP Report, p. 41, No. 44]

Priorities developed in this evaluation process should be used to guide the development of new RFAs by the ICDs.

Current Status

The ICDs develop new RFAs and PAs in response to the scientific priorities identified in the annual update of the NIH Plan for HIV-Related Research. Similarly, some recent RFAs and PAs reflect priorities identified by the NIH AIDS Research Program Evaluation Task Force, for example, NIDA's PA on DU MSM.

Future Actions

It is expected that, to the extent the priorities developed by the Task Force are agreed to by the ICDs, they will be reflected in the FY 1999 NIH Plan for HIV-Related Research and will help shape the formulation of new PAs and, where necessary and appropriate, new RFAs.

Recommendation 143 [Behavioral, Social Science, and Prevention Research ARP Report, p. 41, No. 45]

Study section composition should be informed by scientific priorities identified through this and other OAR processes. Study sections should be briefed regularly by OAR and ICD program staff on the scientific priorities identified through OAR processes.

Recommendation 144 [Behavioral, Social Science, and Prevention Research ARP Report, p. 41, No. 46]

Study sections should review grants for the degree to which they meet the scientific priorities established through this and other OAR processes.

Please refer to the NIH response to Recommendation 6.

Recommendation 145 [Behavioral, Social Science, and Prevention Research ARP Report, p. 42, No. 47]

In the next planning cycle, the Behavioral and Social Science Coordinating Committee should define not only priorities but also criteria for determining whether or not grants meet these priorities.

Current Status

The Coordinating Committee identifies scientific priorities and strategies for HIV-related behavioral and social science. The review process determines the scientific relevance of individual grants. At this point, the review process does not and cannot include consideration of how grants specifically meet the scientific priorities in the Plan.

In addition, please refer to the NIH responses to Recommendations 44–46.

Recommendation 146 [Behavioral, Social Science, and Prevention Research ARP Report, p. 42, No. 48]

The NIH should eliminate the "triage" mechanism implemented in the recently revised grant review process.

Current Status

NIH has received comments both for and against the "triage" or streamlined review process for grants. The balance of comments has favored retaining streamlining procedures. The DRG would welcome discussions of the specific problems believed to result from the process of the streamlined review of AIDS applications and would attempt to address these in an appropriate fashion. However, because streamlined review has become a trans-NIH standard and cannot readily be displaced on an *ad hoc* basis, it would instead need to be considered in a broader context.

Future Actions

The DRG will reassess comments received from ICDs whose experience with streamlined review has been problematic and seek methods for addressing them within the current system.

Recommendation 147 [Behavioral, Social Science, and Prevention Research ARP Report, p. 42, No. 49]

The Panel strongly recommends that the OAR, in cooperation with the ICDs and through the Coordinating Committee process, develop guidelines for coding AIDS research by scientific areas, and that these guidelines be used across future fiscal years to ensure that

it will be possible to trust analyses of funding by areas of science and objectives, and to ensure that multiyear analyses will be possible.

Please refer to the NIH responses to Recommendations 44–46.

Recommendation 148 [Behavioral, Social Science, and Prevention Research ARP Report, p. 43, No. 50]

Expedited funding should be made available to projects seeking to evaluate naturally occurring social or legislative changes.

Current Status

NIH agrees with the Panel that it is important to be prepared to study the impact of social or legislative changes that emerge from or affect HIV-related events. Individual ICDs currently are soliciting or already supporting projects that evaluate naturally occurring social or legislative changes. For example, NIDA supports research that evaluates the implementation of local NEPs and changes in State pharmacy laws related to the purchase of sterile syringes. In addition, the OAR Discretionary Fund may be used to support projects of an emerging nature, including those that propose to study emergent social and policy changes, with the proviso that such projects are adequately peer reviewed and submitted by the appropriate ICDs. This mechanism allows for funding to be made available in an expedited fashion.

Individual ICDs will continue to support this research as relevant and appropriate to their missions. OAR will continue to accept proposals from the ICDs for discretionary funding of critical and timely social and policy-change research related to HIV infection and AIDS. At the same time, there are resources within existing mechanisms to address emerging opportunities. For example, NIAID-supported HIVNET investigators in Thailand were well positioned to study the impact of the Thai Government's rigorous condom promotion program on HIV transmission. Also, the NIMH-funded CFARs contain cores with strong community ties that should be able to provide resources for studying emerging social or legislative changes in their areas.

Future Actions

The OAR Discretionary Fund will continue to be available to support emerging research projects to address social or legislative changes.

Recommendation 149 [Behavioral, Social Science, and Prevention Research ARP Report, p. 43, No. 51]

The OAR should target funds to ICDs for secondary analysis of existing datasets.

Current Status

Population-based studies and prevention trials supported by NIH have accumulated data and public domain data sets suitable for secondary analysis. Some ICDs, notably NICHD, have taken leadership roles in this area, archiving existing data sets concerning HIV-related sexual behaviors and promoting secondary analysis of such data. Though analyses of these data sets have already been undertaken and publications have resulted, much more analysis can be undertaken. The ICDs agree with the Panel recommendation that funds used for secondary analysis of existing data sets would be productive for the field. Conducting secondary analysis of data sets would provide a clearer perspective on progress made to date in population-based studies and prevention trials and on gaps in the current knowledge.

Future Actions

ICDs will identify available data sets, particularly those in the public domain, and utilize existing PAs or amended PAs to encourage the research community to begin to plan for more secondary analysis. OAR Discretionary Funds may be made available for this purpose.

In addition, please refer to the NIH response to Recommendation 41.

III. REVIEW OF SELECTED ICD PROGRAMS IN BEHAVIORAL, SOCIAL SCIENCE, AND PREVENTION RESEARCH

Recommendation 150 [Behavioral, Social Science, and Prevention Research ARP Report, p. 43, No. 52]

NIDA should reverse the proportions of its treatment research portfolio and its harm reduction portfolio to give greater weight to the latter.

Current Status

Since the inception of its AIDS program, NIDA has recognized the importance of HIV prevention research and has invested a sizeable proportion of its AIDS budget to the development and evaluation of HIV prevention strategies. The HIV prevention research program includes a range of strategies including drug abuse treatment, interventions in other medical and social service settings, community outreach, and needle hygiene and exchange programs.

As noted in the Behavioral, Social Science, and Prevention Research Area Review Panel report, the importance of drug abuse treatment as an AIDS prevention strategy was recognized early in the AIDS epidemic. The Congress designated AIDS funds specifically to support research to improve drug abuse treatment effectiveness and research to improve drug abuse treatment continues to be a major thrust of NIDA's HIV prevention research program. As further noted by the Panel, NIDA has established criteria to ensure that AIDS funds are used to support only treatment research that is directly relevant to the reduction of AIDS risk behaviors in populations at high risk for HIV infection/transmission, and the Institute is stimulating development of behavioral and pharmacological treatment strategies that explicitly target risk behaviors.

Although this recommendation suggests a dichotomy between types of approaches, NIDA considers it more appropriate to regard prevention approaches as forming a continuum. Progress in any behavioral intervention informs and contributes to progress across the continuum of interventions.

Future Actions

NIDA is committed to maintaining a balanced HIV prevention program; it will continue to stimulate research across the continuum and to allocate funds across the continuum depending on current research opportunities and public health needs.

Recommendation 151 [Behavioral, Social Science, and Prevention Research ARP Report, p. 48, No. 53]

NIDA should support a "second generation" of studies related to the operations and the impact of needle/syringe-exchange programs on individual participants and communities. The relationship between such programs and other HIV prevention services (including drug treatment) should be particularly encouraged.

Current Status

NIDA has supported and will continue to support research on NEPs to test their efficacy and effectiveness as part of a continuum of HIV prevention interventions targeting drug users. NIDA will continue to study how these programs can and should be linked to other health and drug abuse services as such services are often included in NIDA research.

Individuals recruited into HIV prevention research trials receive preliminary HIV and risk-reduction education and are offered voluntary HIV testing, treatment referral information, and if elected, pre- and posttest counseling. Seronegative and sero-unaware subjects are typically provided with HIV test results, a discussion of risk reduction and the meaning of test results, a review of HIV-related prevention measures, HIV-related literature, and non-HIV-related service referrals. Seropositive subjects typically receive test results, an explanation of positive test results, medical treatment advice stressing benefits of early intervention, and literature including HIV-related referrals and non-HIV-related service referrals, as appropriate. HIV-related referrals include a local referral list to drug treatment agencies (if available) and a local referral to HIV prevention and testing agencies. Trial participants also may be provided information regarding the location and operation of drug treatment agencies, anonymous HIV testing sites, shelters, food and clothing banks, and welfare services.

Future Actions

NIDA has begun a program of research on issues including the linkages between NEPs with drug treatment and other social and medical service providers, component analyses of the services generally provided in NEPs, and evaluation of NEPs integrated with other HIV risk-reduction strategies, e.g., the impact of prevention/intervention messages and the diffusion of information about needle/syringe hygiene procedures.

Recommendation 152 [Behavioral, Social Science, and Prevention Research ARP Report, p. 48, No. 54]

> *NIMH should allocate its AIDS resources in Behavioral and Social Science Research in better accord with the priorities of the NIH Plan for HIV-Related Research, giving a greater proportion to Primary Prevention/Intervention Research.*

Current Status and Future Actions

NIMH has supported a broad research program in AIDS research ranging from neuroscience to AIDS behavioral prevention. NIMH has reassigned research where the relationship to AIDS was tangential.

The NIH AIDS Research Program Evaluation Task Force reviewed programs from FY 1990 through FY 1994. Since that time, the NIMH AIDS portfolio has realigned the percentage of support for different areas.

NIMH has issued new PAs to attract new investigators and research projects in the primary prevention/intervention research area. Currently, the percentage of AIDS prevention research has grown to 55 percent, of which the majority is focused on primary prevention.

Recommendation 153 [Behavioral, Social Science, and Prevention Research ARP Report, p. 50, No. 55]

> *NIMH should support preventive interventions with a broader range of theoretical perspectives from the behavioral and social sciences than currently is present.*

Current Status

Over the past several years, a number of NIMH and other PHS agencies have developed an effective AIDS prevention research program. NIMH-supported investigators have established the efficacy of intensive face-to-face group interventions based on social-cognitive and cognitive behavioral principles that produce changes in sexual practices in samples of at-risk gay and bisexual men, adolescents, minority women, and chronically mentally ill, homeless men and women.

NIMH concurs that the preponderance of AIDS prevention research is based on Social Learning Theory and other cognitive behavioral approaches. The NIMH Phase III high-site prevention trial, the results of which will be unblinded in May 1997, is also based on a cognitive behavioral approach.

Future Actions

NIMH, in collaboration with other PHS agencies, intends to implement a new AIDS prevention initiative that will specifically call for innovative, new theoretical approaches and will solicit the expertise of social scientists.

Recommendation 154 [Behavioral, Social Science, and Prevention Research ARP Report, p. 50, No. 56]

> *NIMH should expand its strong focus on primary prevention trials to support more community- and social (including legal and policy)-level interventions (rather than small-group risk reduction interventions) and to increase emphasis on the maintenance of behavior change.*

Current Status and Future Actions

Community-based prevention campaigns using community mobilization, popular opinion leaders, social marketing, and other approaches have been demonstrated to be effective, cost-saving approaches to prevent the further spread of HIV infection. NIMH agrees that a major research effort to develop and test community-level behavior change interventions that are cognizant of hierarchies of power and able to reach understudied, at-risk populations is needed. NIMH will

support research to identify the determinants and mediators of HIV-related risk behaviors that can be addressed in community-level interventions.

Recommendation 155 [Behavioral, Social Science, and Prevention Research ARP Report, p. 50, No. 57]

NIMH should encourage multilevel sustained behavior change intervention models that draw upon many different theories and intervention modalities rather than emphasize "pure tests" of single theories. The review process must be sensitive to and reflect recognition of the merits and validity of this approach.

Current Status

NIMH recognizes that a multilevel approach to behavioral change intervention models is extremely valuable in assisting individuals to change behavior and to maintain low-risk behaviors. Many of the studies that use public opinion leaders rely on role modeling and persuasion to change community norms in order to initiate and maintain low-risk HIV behaviors. NIMH also has taken the lead in developing a rigorous family and HIV/AIDS research program that utilizes the family and community in developing AIDS prevention programs.

Future Actions

NIMH intends to meet with SRAs and IRGs to which the majority of AIDS research applications are referred in order to discuss new developments in AIDS research. Also, the concept of phases of behavioral research will be shared with them in order to validate the utility of novel, cutting-edge research projects that represent a gamble but a potential breakthrough in AIDS research.

Recommendation 156 [Behavioral, Social Science, and Prevention Research ARP Report, p. 50, No. 58]

NIMH should broaden its support of social science research, including studies of social, policy, and legal change related to HIV prevention and cost-effectiveness and cost-benefit analyses of various HIV intervention modalities.

Current Status

NIMH has two AIDS research centers with "cores" that focus on policy issues. The investigators in these cores provide consultation to other Center investigators and at other universities.

NIMH has convened two meetings of experts on the topic of economic evaluation of AIDS prevention programs. A PA on "Integrating Economic Evaluation into AIDS Prevention Research" has been developed and will shortly be released. A grant has been funded to conduct a retrospective study of the cost-effectiveness of an effective AIDS prevention program with women.

NIMH is cofunding the AHCPR HIV Cost, Services, and Utilization Study, which is prospectively following a thousand HIV-seropositive patients in primary care settings. The mental health component is prominent in the study, and a cost-benefit analysis is being conducted.

Future Actions

NIMH intends to develop a new research initiative focused on social, legal, and policy strategies in AIDS prevention early in 1997.

Recommendation 157 [Behavioral, Social Science, and Prevention Research ARP Report, p. 52, No. 59]

NIAID should not use HIVNET to conduct social and behavioral intervention research unless or until the appropriate expertise can be integrated into the HIVNET governance and review processes.

Current Status

In June 1996, NIAID and OAR convened a multidisciplinary panel of experts to conduct a review of HIVNET organization, governance, research, and funding. This review included participation from other ICDs with research expertise relevant to HIVNET's activities. Panel members expressed confidence in HIVNET. They found the scientific plan and program of research to be sound. In addition, the panel noted that there had been considerable progress and maturation of HIVNET since the time of the NIH AIDS Research Program Evaluation Task Force process. The panel provided a number of constructive recommendations to further improve HIVNET, including the following recommendations specifically related to behavioral research:

- HIVNET should be continued and should give priority to its original mission, which is to provide the capacity for prompt and scientifically based assessment of vaccine efficacy both domestically and internationally.

- HIVNET must continue to maintain a strong high-disciplinary approach to maintain or develop its capacity for evaluating both vaccine and nonvaccine interventions.

- For non-vaccine-based activities, prioritization and implementation plans should include clearly articulated guidelines for the choice of product or interventions. For microbicides and perinatal transmission research, these guidelines should include the potential global availability of products, biological endpoints, and individual rather than community intervention strategies. Behavioral research should focus on descriptive or methodological studies essential for the conduct of vaccine trials. When promising behavioral interventions have been identified as suitable for testing in HIVNET, they should be tested using HIV infection as the trial outcome measure.

In response to the recommendation of the NIH AIDS Task Force evaluation and the HIVNET review panel, the OAR organized a meeting including NIAID and NIMH program staff, HIVNET investigators, and scientists funded by NIMH. The purpose of this meeting was to develop

criteria for studies of behavioral interventions with clinical endpoints. This group identified a set of issues, including sample size, power, and ethical issues, that must be resolved for each particular trial. HIVNET and NIMH investigators are now in the process of developing a protocol for a specific intervention.

Recommendation 158 [Behavioral, Social Science, and Prevention Research ARP Report, p. 54, No. 60]

NICHD should support more HIV preventive intervention research focused on youth most vulnerable to HIV infection and should develop mechanisms for disseminating findings from such research to communities and service organizations.

Current Status

NICHD's first priority and its unique contribution in this area remain its basic behavioral and social science research, which provides the basis for developing HIV preventive interventions. For instance, NICHD has successfully supported several basic behavioral STD/AIDS prevention studies that have generated a growing body of information describing the antecedents to risk behaviors and the sexual/contraceptive practices of youth that can be targeted through interventions. Results from studies targeting minority populations have demonstrated that short-term interventions can change compliance for protected intercourse in teens; availability of condoms does not increase the frequency of intercourse in teens; and the best predictor of reduced sexual activity is school performance. NICHD-supported researchers further used this information to design and test various behavioral interventions to determine which strategies are most effective in helping youth modify behaviors that place them at risk for STD/HIV infections and unwanted pregnancies. To date, some of the tested interventions show promising results; however, additional research needs to be performed before the interventions are ready for widespread public use.

Based on the experience to date, further research is needed to (1) link the findings of different behavioral studies from various disciplines to develop the optimum strategies for sustaining changes; (2) develop ways to utilize the social networks of youth to strengthen interventions targeting sexual behavior; and (3) test interventions targeting middle childhood, an important developmental stage for preventing the advent of many risky behaviors including those that place children at risk for acquiring HIV. In addition, research is needed to examine approaches to dissuade youth from engaging in high-risk behaviors (i.e., unprotected sex) and to use methods that prevent both STD/HIV infections and unwanted pregnancies. New intervention initiatives need to have new theoretical formulations; hence, basic research is needed to build and strengthen available behavioral theories for designing interventions. NICHD also is very interested in supporting studies to translate these findings into theoretically sound projects. To accomplish this, however, means having to overcome many barriers that characterize such research efforts.

For example, researchers will need to overcome such barriers as (1) obtaining parental, community, and political support for introducing explicit messages about protective sexual behavior where youth are involved, (2) resolving confidentiality and liability issues associated with recruiting youth from vulnerable populations, (3) recruiting health and service agencies to

participate in designing and implementing intervention research, and (4) identifying where the greatest opportunities exist for evaluating intervention outcomes. Despite the difficulties, these issues can be addressed by working with community groups to foster a common understanding of goals, developing stronger linkages to other private and public groups working on community-level AIDS intervention efforts, and adequately funding projects to invest the effort needed to address the many gatekeeper and ethical issues.

Administrative issues also must be resolved. For example, many HIV/AIDS intervention projects are ultimately referred to other ICDs. To address this concern, the NICHD recently proposed that the NIH referral guidelines be amended to state that research on HIV-related sexual behavior not focused on mental health issues should be referred to NICHD in addition to those applications on social, psychological, and economic factors affecting sexual behavior. The status of this proposal is unknown. In addition, other efforts to expand HIV/AIDS intervention research beyond the current level would require NICHD to increase the number of staff or full-time equivalents (FTEs) dedicated to this new effort. However, given the current freeze on FTEs and research management and support funds, immediate increases are unlikely to occur. Meanwhile, NICHD is poised to do more research on behavioral interventions by stronger collaborations with NIMH on such studies. This effort may include initiating discussions about research priorities and collaborating in planning and cofunding projects.

Future Actions

As noted above, while NICHD remains committed to supporting the basic research that undergirds HIV preventive intervention research, NICHD also is very interested in starting new intervention projects and leveraging its resources by cosponsoring projects with other ICDs. Some of the NICHD current and proposed activities are described below.

- NICHD recently funded an STD/HIV prevention intervention study targeting young gay and bisexual Hispanic men. This study will take place in two large U.S. cities.

- NICHD has implemented several interventions to test STD/HIV prevention methods. With funding from the Office for Research on Minority Health, NICHD has managed a set of cooperative agreements to design, implement, and evaluate community-based interventions to deter the spread of STDs, violence, and pregnancy in minority youth. In another separate NICHD-supported study, investigators tested a high-ethnic, school-based, HIV prevention curriculum and an office-based intervention that used special educational materials to help adolescent health practitioners discuss HIV-related risk behaviors with young clients. The data from these projects are now being analyzed. Early data suggest that explicitly addressing the sexual and contraceptive needs of young, unmarried individuals may be the most effective deterrent to STD transmission. While the scientific evidence supports this finding, communities may be unable to adopt the message for political reasons. NICHD project investigators are currently planning the next steps in these studies and considering the best ways to disseminate the findings.

- Data collection is complete for both rounds of the recent Add-HEALTH study, and the first reports are expected in early 1997. The data identify the determinants of risky

behaviors that may expose youth to STD/HIV pathogens, characterize the development and progress of sexual partnerships among youth, and provide a comprehensive view of youth health (including sexual) behaviors and outcomes. These data should provide one of the most current and comprehensive databases yet available for designing programs and interventions to improve adolescent health and prevent HIV infection among sexually active teens. The data will be made available to U.S. researchers, educators, health care providers, and community groups to further research (including intervention studies) and for use at the local level.

- NICHD is planning to target middle childhood in intervention studies assessing how normative risk-taking patterns may go awry for vulnerable children who, for example, engage in sexual or drug use behavior that may expose them to HIV infection. These studies will be supported through a PA or RFA. Parenting skills will be a particular focus of this initiative, using schools and neighborhoods as the unit of analysis. NICHD plans to engage in several activities to help disseminate any significant findings from funded projects. Grantees would be expected to involve community members invested in the project, including representatives from community-based organizations, parents, school officials, and targeted subjects. NICHD also plans to create a network of funded PIs and community members who will come to the NIH annually to give project input and present progress reports and summaries of their findings. The proceedings from the final meeting would be published either in a journal or book. As practical implications emerge from these studies, NICHD will develop summaries, overviews, and pamphlets—akin to those it developed for learning disabilities—that would be made available to communities to help them establish scientifically based intervention programs.

- Early in 1997, NICHD will issue a PA calling for research in several areas relating to sexual behaviors. A special emphasis will be placed on the dual use of methods to prevent pregnancy and disease, as well as intervention studies from high-disciplinary perspectives. While the issue of dual use applies to the majority of couples, NICHD recognizes that related behavioral questions are particularly complex for younger men and women, especially when different social, ethnic, and contextual factors are considered. Staff will encourage applications for interventions that focus on these groups. The PA also will encourage intervention studies that focus on youth whose behavior makes them most vulnerable to HIV transmission and that involve community-based organizations in the design and implementation of the studies.

- As NICHD is able to fund more intervention studies, health researchers from community-based organizations and public health practitioners will be invited to serve on relevant scientific advisory boards.

- In July 1996, NICHD funded a grant to test an intervention designed to examine whether and how women use STD clinics (settings frequently populated by younger women and those at increased risk for acquiring HIV infection) as a gateway for family planning services as well.

- NICHD also recently funded a study to examine the utility of social networks in preventing STDs. Data will be collected from young clients in Baltimore STD clinics. This study has an intervention component that will target the client's social network to determine which points are most effective in HIV prevention efforts.

Recommendation 159 [Behavioral, Social Science, and Prevention Research ARP Report, p. 55, No. 61]

NIAAA should be commended for its effort to support HIV-related behavioral research with such a small budget. However, a better balance should be struck between pre-intervention and primary prevention/intervention research, requiring that greater resources be devoted to the latter over the next few years.

Current Status

NIAAA agrees with the Panel's recommendation that it should fund an increased number of interventions among alcohol-using, -abusing, and -dependent populations that are at risk of HIV infection or who have become infected.

During the NIH AIDS Research Program Evaluation Task Force process, the NIAAA behavioral research portfolio contained 8 to 10 preintervention grants and 3 or 4 primary prevention/ intervention grants. To increase the number of primary prevention/intervention grants by 5 to 10 to "change the balance of grants" would cost approximately $1.5 to $3 million at an average total grant cost of $300,000. This change can be most immediately accomplished by preparing and releasing an RFA in 2 consecutive years with an average of $1 to $1.5 million per year allocated to this initiative. The advantage of this approach would be to assemble relevant reviewers with specific expertise in these areas to focus on alcohol and HIV interventions.

Future Actions

NIAAA concurs with the recommendation that a better balance is needed between the NIAAA preintervention and primary prevention/intervention research. Three possible strategies for addressing this imbalance are being implemented:

- The first strategy is to release an RFA in FY 1997 entitled "Developing and Testing of Alcohol-Related HIV Preventive Interventions."

- The second strategy is to develop or augment interventions proposed within the context of larger clinical or epidemiological studies such as HIVNET. A working group has been approved and will be convened in FY 1997 to generally discuss alcohol/AIDS interventions and specifically to design and evaluate the feasibility of an intervention within the context of HIVNET.

- The third strategy will be to supplement ongoing alcohol intervention grants to include HIV-infected or at-risk populations in their studies as a significant subpopulation that may be contrasted with more traditional alcohol-related risk groups.

Recommendation 160 [Behavioral, Social Science, and Prevention Research ARP Report, p. 55, No. 62]

NIAAA and other Institutes such as NIDA or NIMH should develop methods to foster greater integration and collaboration on intervention (as well as basic science) research on the relationship between alcohol, other drug use, and HIV transmission risk. These could include (1) joint development and support of RFAs; (2) representatives from other NIH Institutes (such as NIDA or NIMH) participating in program reviews for NIAAA; (3) specific RFPs, jointly sponsored, to encourage intervention research related to alcohol and drug use and HIV transmission risk behaviors and their contexts (particularly with respect to drug injectors and crack cocaine users).

Current Status

NIH recognizes the importance of collaborative research on the intersection of alcohol use, other drug use, and risk-taking behaviors. In the past, NIAAA has collaborated with other ICDs in soliciting applications through the use of RFAs and PAs and is currently collaborating with NIAID in the analysis of alcohol-related data and the development of potential interventions within the context of HIVNET. At present, NIAAA is conducting its HIV/AIDS grant reviews through the appropriate committees at DRG. NIDA and NIMH grantees as well as other ICD grantees participate as both regular review members and as *ad hoc* reviewers on these committees.

Future Actions

While no joint development or support for RFAs has been proposed, future cooperation is anticipated, particularly where scientific and clinical issues overlap. Areas of potential collaboration include the study of HIV risk among populations dually diagnosed with substance abuse and mental health problems. Specific requests for proposals will be considered to study both comorbid substance-use disorders and co-occurring substance-use and psychiatric disorders prevalent in at-risk populations.

Recommendation 161 [Behavioral, Social Science, and Prevention Research ARP Report, p. 57, No. 63]

The Panel recommends that NIA resume its commitment to HIV/AIDS and aging research by issuing its own PA, RFA, or RFP, in addition to participating in those initiated by other ICDs.

Current Status and Future Actions

NIA is considering publication of a PA on AIDS and Aging in early FY 1998. To prepare for and to generate ideas and recommendations helpful in developing this solicitation, NIA plans to convene a workshop on behavioral, social, and clinical aspects of AIDS and aging research in

FY 1997. In addition, NIA intends to issue a PA for small grants in FY 1997; AIDS and Aging will be featured among a limited number of topics in this solicitation.

Etiology and Pathogenesis Area Review Panel Recommendations

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CROSSCUTTING RECOMMENDATIONS FROM THE EXECUTIVE SUMMARY

Recommendation 162 [Etiology and Pathogenesis ARP Report, p. 1, No. 1]

Increased emphasis on investigator-initiated research through doubling of the R01 pool of funding.

Please refer to the NIH response to Recommendation 178.

Recommendation 163 [Etiology and Pathogenesis ARP Report, p. 1, No. 2]

Continued, but more selective, use of RFAs with set-aside funding in critical areas of research not addressed by the R01 mechanism; these critical areas should be identified in an ongoing conjoint effort of the ICDs, OAR, scientific advisors, and community representatives.

Please refer to the NIH response to Recommendation 179.

Recommendation 164 [Etiology and Pathogenesis ARP Report, p. 1, No. 3]

Increased support to encourage long-range discovery research and the entry of both new and distinguished established scientists into the field.

Please refer to the NIH response to Recommendation 181.

Recommendation 165 [Etiology and Pathogenesis ARP Report, p. 1, No. 4]

Increased focus on understanding the basic immunology of infected and uninfected human beings and primates and on efforts to attract immunologists to the field.

Please refer to the NIH responses to Recommendations 20, 182, and 183.

Recommendation 166 [Etiology and Pathogenesis ARP Report, p. 1, No. 5]

Redirection of funding away from research projects, both extramural and intramural, that are judged to be of lesser quality or relevance.

Please refer to the NIH response to Recommendation 185.

Recommendation 167 [Etiology and Pathogenesis ARP Report, p. 1, No. 6]

Redirection of funding for research or infrastructure currently designated as AIDS-related but which does not meet the rigorous criteria called for by the Panel.

Please refer to the NIH response to Recommendation 186.

Recommendation 168 [Etiology and Pathogenesis ARP Report, p. 1, No. 7]

Open competition and expert peer review to increase access to funding at Regional Primate Research Centers (RPRCs) and the neuro-AIDS centers for training and research.

Please refer to the NIH responses to Recommendations 37–39.

Recommendation 169 [Etiology and Pathogenesis ARP Report, p. 1, No. 8]

Restoration of resources to the most relevant nonhuman primate model.

Please refer to the NIH response to Recommendation 200.

Recommendation 170 [Etiology and Pathogenesis ARP Report, p. 1, No. 9]

Greater involvement of the extramural scientific community in the design of natural history studies to engender hypothesis-driven collection of specimens.

Please refer to the NIH response to Recommendation 42.

Recommendation 171 [Etiology and Pathogenesis ARP Report, p. 1, No. 10]

Separation of collection of specimens from access to specimens by all qualified investigators.

Please refer to the NIH response to Recommendation 42.

Recommendation 172 [Etiology and Pathogenesis ARP Report, p. 2, No. 11]

Open competition and comparable criteria for funding for all mechanisms and programs.

Please refer to the NIH response to Recommendation 189.

Recommendation 173 [Etiology and Pathogenesis ARP Report, p. 2, No. 12]

Improved peer review, from the composition of the study sections to shared oversight by the ICDs and OAR.

Please refer to the NIH response to Recommendation 192.

Recommendation 174 [Etiology and Pathogenesis ARP Report, p. 2, No. 13]

Improved management and AIDS focus achieved by fully vesting OAR with the fiscal and scientific authority to coordinate the total NIH AIDS effort, intramural and extramural, but operating by regularly and systematically soliciting advice from leading scientists and community representatives in the formulation and evaluation of its plans for pathogenesis research.

Please refer to the NIH response to Recommendation 187.

Recommendation 175 [Etiology and Pathogenesis ARP Report, p. 2, No. 13]

Improved management and AIDS focus achieved by restructuring the AIDS information retrieval system.

Please refer to the NIH response to Recommendation 43.

Recommendation 176 [Etiology and Pathogenesis ARP Report, p. 2, No. 13]

Improved management and AIDS focus achieved by devising a mechanism to define AIDS-related research (ARR) that is both rigorous and evolving in response to new scientific priorities.

Please refer to the NIH response to Recommendation 44.

RECOMMENDATIONS FROM THE REPORT

Recommendation 177 [Etiology and Pathogenesis ARP Report, p. 4, No. 1]

Improve the scientific portfolio: programs and human and fiscal resources.

The Panel discussed at length mechanisms to develop and maintain an optimal and balanced scientific portfolio, launch new programs, and allocate resources. The Panel believes that the mechanisms and process that shape the scientific portfolio could also be used to serve other important objectives: attracting new highly qualified junior investigators and leading senior investigators in other fields to AIDS research, and providing more training opportunities for the most promising students and postdoctoral fellows.

Please refer to the NIH responses to Recommendations 179 and 181.

Recommendation 178 [Etiology and Pathogenesis ARP Report, p. 5, No. 1a]

Double the support for unsolicited investigator-initiated AIDS research (even if this results in different pay lines for AIDS and non-AIDS research).

Current Status

NIH agrees with the Panel that a significant increase in unsolicited investigator-initiated research is the optimal approach to foster basic research on HIV/AIDS. In the last few years, NIH has worked to steadily increase support for unsolicited investigator-initiated AIDS research. NIAID has increased funding of investigator-initiated research by 9.3 percent from FY 1994 to FY 1995. Current projections indicate that funding in FY 1996 will have increased 17.7 percent since FY 1994.

NCI has recently undertaken a process to redirect funds allocated to its intramural and extramural programs in order that the ratio of funding for these two programs is more in line with that of the other ICDs. As a result of this effort, an estimated 30-percent increase in extramural AIDS dollars is projected for FY 1996. NIMH allocated 50 percent of its budget in FY 1996 to fund investigator-initiated research. It continues to encourage and promote the use of the R01, the R29, as well as the R03 (small grant) mechanism above all other funding mechanisms available. Almost all of NIDA's AIDS-related etiology and pathogenesis grants are investigator-initiated, most designated R01s.

NICHD support for AIDS-related R01 grant applications also has seen a steady increase over the last 3 fiscal years. From FY 1994 to FY 1995, R01 support has increased by 13 percent and from FY 1995 to FY 1996 by 17 percent. Some of these increases have been made possible through careful use of funding in a so-called "discretionary zone," whereby highly meritorious R01 grant applications that are just beyond the pay line are funded with approval of the NICHD Council.

NICHD has determined that a number of contracts focused on HIV and AIDS-related areas will be permitted to expire and not be recompeted in order to ensure increasing availability of funds to support R01 grants.

Future Actions

Efforts will continue in every ICD to increase funding available for R01 grants. Working with OAR, the NIH ICDs will continue to increase funding for unsolicited investigator-initiated research as their budgets allow, taking into consideration scientific merit, linkage to the strategic NIH Plan for HIV-Related Research, and issues of programmatic relevance.

Recommendation 179 [Etiology and Pathogenesis ARP Report, p. 5, No. 1b]

> *Use RFAs with set-aside funding selectively, both to focus attention on important areas of pathogenesis research and to bring established or new high-caliber scientists into the field.*

Current Status

NIH recognizes that RFAs have played an essential and crucial role in directing AIDS research at the onset of the epidemic. The use of the RFA mechanism has been highly successful in drawing both senior basic scientists and new investigators into the AIDS field and in focusing attention on HIV pathogenesis. However, 15 years into the epidemic, NIH believes those funding mechanisms associated with a greater dependence on investigator creativity will better accomplish the goal of promoting high-quality and relevant AIDS research.

The identification of critical areas of understudied and underfunded research is accomplished by OAR and NIH through the development of the NIH Plan for HIV-Related Research. This planning process includes participation of scientific experts from academia, industry, Government, and foundations as well as from the affected communities. Through this process, a consensus is developed regarding the direction and priorities for AIDS research. In addition, the identification of important areas of research that are underfunded ("programmatic gaps") is accomplished within a number of ICDs using their own HIV/AIDS research agendas. These agendas are formulated in cooperation with Institute councils and other outside advisors and are in concurrence with OAR goals. As an example, with the help of expert *ad hoc* advisors, NIAID's ARAC explores scientific opportunities with the Institute's extramural divisions to develop potential concepts and determine whether a concept should be developed into a PA or an RFA. This continuous process of identifying priorities in AIDS research has resulted in a substantial decrease of RFAs in the last few years.

NIH ICDs, including NIAID, NCI, NIDA, NIMH, NICHD, and NHLBI, will continue to increase investigator-initiated research through R01s and PAs in lieu of RFAs. These PAs include a commitment that NIH will award grants in the targeted area. This policy appeals to applicants, who gain the benefits of investigator-initiated research, including multiple receipt dates, multiple funding mechanisms, review by the DRG, and a commitment to fund research in the stated area.

NIH is funding highly meritorious applications with percentiles within the pay line and beyond it, when necessary, to build a comprehensive and responsive research portfolio. The use of PAs ensures open competition and comparable criteria for review and funding. The possibility of establishing mechanisms by which several ICDs can participate in the same PA is also being entertained in view of the increasing need for multidisciplinary approaches to important scientific priorities. As an example, NCI, NIDA, NIMH, NICHD, and NHLBI are collaborating with NIAID to change the announcement for the recompetition of the CFAR program from an RFA to a PA.

Future Actions

PAs will be issued more often in the future, although effort must be directed to assuring the research community that the use of PAs signals NIH's intention to focus and commit funding in the areas identified in the PAs. RFAs will be used only when review criteria for the initiative are not standard for DRG and for critical areas of research which cannot be properly addressed by a PA.

Recommendation 180 [Etiology and Pathogenesis ARP Report, p. 6, No. 2]

Enhance the emphasis on long-range discovery research in areas of highest priority, especially human immunology.

Recommendation 181 [Etiology and Pathogenesis ARP Report, p. 6, No. 2a]

Use MERIT and similar awards (e.g., the Javits Award) and create incentives to encourage long-range and innovative research.

Current Status

NIH recognizes the need to foster critical research areas that may require long-term perspectives. This represents an NIH-wide challenge that is not limited to AIDS research.

In the last few years, NIH has decreased support of Method to Extend Research in Time (MERIT) awards while steadily increasing support for unsolicited investigator-initiated AIDS research. MERIT awards compete for the same funds allocated to investigator-initiated grants. The constraints placed on the length and size of the MERIT awards have had an impact on the balance between serving short-term and long-term goals and usually have resulted in the de-emphasis of MERIT awards across NIH in times of limited funding levels. Currently, both the investigator's track record and the quality of the research proposal are the review criteria, and reviewers can place different weights on the various criteria for different applications.

NIH also is encouraging innovative research by experimenting with a scoring system for R01s that would include separate scores for novelty and potential impact of the proposed research. This will allow the ICDs to assign differential weights to the separate components of the new priority score and make funding decisions accordingly.

Future Actions

NIH will continue to experiment with new mechanisms to enhance long-range and innovative research while maintaining the creativity associated with unsolicited investigator-initiated AIDS research.

Recommendation 182 [Etiology and Pathogenesis ARP Report, p. 6, No. 2b]

Convene a series of meetings of expert non-AIDS and HIV/SIV immunologists to consider ways of engaging immunologists in the effort to address the critical issues and to overcome the challenges of studying the immune systems of genetically complex humans and nonhuman primates.

Current Status

NIH recognizes the critical need to make further progress in understanding basic aspects of the human immune system. The mouse model system has been instrumental in deciphering many basic aspects of the immune system function. Unfortunately, not all of the findings can be directly translated to the human system because of its inherent complexity and heterogeneity. As a result, studies of HIV/SIV immunology in human and nonhuman primate models are underrepresented in the NIH scientific portfolio.

Future Actions

OAR will, with the help of relevant ICDs, convene a series of workshops to address the scientific needs highlighted by this recommendation. These workshops will be chaired by AIDS and non-AIDS expert immunologists and will be instrumental in the development of the overall AIDS research agenda. The first workshop will be convened in late 1997 to address issues about T-cell repopulation following therapeutic interventions that have significant effects on CD4+ T-cell numbers. These meetings will serve to encourage new collaborations between investigators with complementary expertise and, most important, attract new investigators to this area of AIDS research.

NIAID, the ICD with the major research portfolio in human immunology, is working to achieve the goal articulated in this recommendation. In FY 1997 NIAID will sponsor a workshop at the American Association for the Advancement of Science on “Genetic Resistance to HIV-Infection,” which is expected to attract participation by a number of non-AIDS immunologists. In addition, NIAID will work with the professional immunology societies to communicate current and future research opportunities in HIV/AIDS research.

Recommendation 183 [Etiology and Pathogenesis ARP Report, p. 6, No. 2c]

Provide supplemental funding to attract immunologists into the field.

Current Status

NIH agrees that provision of supplemental funding may be an effective means to attract immunologists into the AIDS research field. Most ICDs allow for competitive supplements to ongoing NIH-funded grants as a mechanism by which investigators in related fields can obtain funds for studies related to HIV/AIDS. In recent PAs, ICDs have made it possible for scientists not currently working in the field of AIDS to collaborate with AIDS investigators by competing for supplemental funds to existing NIH grants.

In addition, NIAID staff have invited scientists who work in related basic fields but who are not active in HIV/AIDS research to all NIAID workshops. By participating in these workshops, investigators outside the HIV/AIDS field have become more familiar with AIDS research.

The CFARs also promote interactions among investigators within and outside of the HIV/AIDS field. Each CFAR funds small developmental projects, open to AIDS and non-AIDS researchers, to facilitate preliminary studies. The availability of core laboratories, reagents, and technical expertise at these sites makes the CFARs ideal locations for non-AIDS researchers to collaborate with AIDS investigators.

Future Actions

NIH will explore new approaches or try to adapt existing funding mechanisms to achieve the goal outlined in this recommendation.

Many ICDs have ongoing programs to supplement grants to train minority researchers and researchers with disabilities. This model could be adapted to provide supplemental funding to support immunologists to carry out AIDS-related research. If any of these mechanisms proves to be effective, it will be improved upon and expanded in the future. NIH also will work closely with DRG in order to increase flexibility and quality of the peer-review process associated with these existing funding mechanisms.

In addition, please refer to the NIH responses to Recommendations 11–13.

Recommendation 184 [Etiology and Pathogenesis ARP Report, p. 6, No. 2d]

Establish consortial approaches between basic immunologists and investigators currently engaged in AIDS research. The anticipated benefits of the consortial mechanisms include overcoming basic immunologists' unfamiliarity with AIDS research and concerns about working with infectious agents; facilitating exchange of ideas, techniques, reagents, and personnel; and increasing the likelihood that postdoctoral fellows will go into AIDS research.

Please refer to the NIH response to Recommendation 20.

Recommendation 185 [Etiology and Pathogenesis ARP Report, p. 7, No. 2e]

Funds from these programs of poor quality, productivity, and relevance should be redirected.

Current Status

NIH strongly endorses the redirection of research funds when the programs they support are found to be of poor quality, productivity, or relevance. NIH believes that the review process for both intramural and extramural programs provides the procedures for discontinuing projects judged to be of lesser quality or relevance. All decisions regarding funding of research projects, both intramural and extramural, are based on the peer-review system. The review of all investigators involves both prospective and retrospective elements to varying degrees. Grant reviews are typically considered prospective, although reviews of renewals are retrospective processes. Primarily, retrospective reviews occur through the review of an intramural scientist (reviewed every 4 years) as well as MERIT awardees (reviewed after 5 or 8 years). All of these processes involve *ad hoc* members and established panels of reviewers (DRG for extramural research programs; Board of Scientific Counselors, consisting of non-Government scientists, for intramural research programs). Funding decisions are thus reached by a balance of independent and ICD peer reviews: the former to determine scientific merit of the research projects and the latter to determine their linkage to the NIH Plan for HIV-Related Research and their programmatic relevance.

The intramural review process has recently changed to become more comprehensive and rigorous. As an example, in response to recommendations expressed in the 1995 report, "A Review of the Intramural Program of the National Cancer Institute" (also known as the "Bishop/Calabresi Report"), NCI initiated a rigorous outside peer review of each intramural program, laboratory, and component project. In less than a year, entire scientific programs have been phased out or realigned with the Institute's priorities. In the past, the intramural program review processes have varied among Institutes. Recently, uniform procedures for reviews have been implemented.

Future Actions

OAR and the ICDs will continue to work with DRG to enhance the extramural review process with the goal of improving the quality, flexibility, and AIDS relevance of AIDS-related grants in accord with the priorities of the NIH Plan for HIV-Related Research. The NIH also will continue to enhance the intramural review process so that it is even more rigorous and comprehensive.

Recommendation 186 [Etiology and Pathogenesis ARP Report, p. 7, No. 2f]

Rigorous guidelines on what constitutes AIDS and ARR will likely free up needed resources.

Current Status

NIH concurs with the recommendation that there is a clear need for a rigorous definition for AIDS-related research. To this end, the OAR Coordinating Committees reviewed the findings and preliminary recommendations of the NIH AIDS Research Program Evaluation Task Force Report and incorporated them into each appropriate scientific area of the FY 1998 NIH Plan for HIV-Related Research. In this Plan, the definition of "investment area" was introduced to take into account scientific areas that would not usually be classified as HIV/AIDS research but would represent basic research topics where additional resources might be expected to provide insights into fundamental aspects of HIV/AIDS.

ICDs develop, within the framework of the NIH Plan and with concurrence from OAR, their own definition of AIDS and AIDS-related research according to their scientific purview. These ICD-specific definitions reflect the broader definition provided by the NIH Plan and help to define research projects that receive AIDS funding. Therefore, all ICD AIDS-related projects are linked to specific objectives in the NIH Plan for HIV-Related Research.

NCI recognized the problems and inconsistencies that occurred prior to FY 1996 with respect to its assignment of OAR Strategic Plan codes to intramural research projects in the area of AIDS pathogenesis, vaccine, and therapeutics research. In October 1995, the NCI Executive Committee reviewed the Institute's AIDS research program and determined that a significant reallocation of resources would take place in FY 1996 within all areas of its intramural and extramural AIDS research programs, along with a reevaluation of the OAR Strategic Plan codes assigned to each project.

Future Actions

NIH, beginning in FY 1999, will use the annual NIH Plan for HIV-Related Research as the formal definition of what constitutes AIDS research. Critical basic research areas defined as investment areas in the FY 1998 Plan will become an integral part of the Plan. The OAR Director and the OAR Coordinating Committees will identify fundamental research areas where support with AIDS funds is expected to advance the overall AIDS research effort. Such targeted areas will be identified as specific strategies under objectives within each area of emphasis. The ICDs will use this definition of AIDS research in coding and reporting their AIDS programs and projects.

Recommendation 187 [Etiology and Pathogenesis ARP Report, p. 7, No. 2g]

> *OAR should establish mechanisms involving the extramural scientific community, such as the annual scientific planning workshops, for open discussion and decision on the portion of the AIDS research budget that would be appropriate to use to support the general costs of biomedical research (matched by services received) and of AIDS research that are nominally designated currently as etiology and pathogenesis.*

Current Status

OAR vigorously and regularly seeks advice from extramural and other non-Government scientists and representatives of the affected communities through their participation in OARAC, OAR-sponsored focus groups, and state-of-the-science workshops. OAR values and relies on such outside input in developing the annual NIH Plan for HIV-Related Research, which is used by the NIH and OAR Directors in carrying out their responsibilities to apportion funds for NIH AIDS-related research.

The OAR Coordinating Committees, composed of Government scientists, develop the first draft of the annual Plan during a series of meetings. Subsequent to review and input from all ICDs, non-Government scientists and community representatives are asked to review the draft Plan and establish the research priorities within it.

For the FY 1998 Plan, the Coordinating Committees reviewed the findings and preliminary recommendations of OARAC's NIH AIDS Research Program Evaluation Task Force and incorporated these insights into each appropriate scientific area. In this particular Plan, the new definition of "investment areas" was introduced to take into account scientific areas that would not usually be classified as HIV/AIDS research but which represent basic research topics where additional resources might be expected to provide important data that could contribute to the understanding of certain aspects of HIV/AIDS. All AIDS-related projects sponsored by the ICDs and funded by AIDS monies are coded according to the Plan.

The combination of advice from the extramural and intramural groups for developing the annual NIH Plan for HIV-Related Research as well as other guidance from OARAC permits the development of a balanced portfolio of research in etiology and pathogenesis.

Future Actions

Beginning in FY 1999, NIH will use the annual NIH Plan for HIV-Related Research as the formal definition of what constitutes AIDS research. Critical basic research areas formerly defined as separate investment areas will become an integral part of the Plan. Such targeted areas will be explicitly identified as specific strategies under objectives within each area of emphasis.

In addition, please refer to the NIH response to Recommendation 44.

Recommendation 188 [Etiology and Pathogenesis ARP Report, p. 7, No. 3]

Improve peer review, quality control, and AIDS focus.

Please refer to the NIH response to Recommendation 2.

Recommendation 189 [Etiology and Pathogenesis ARP Report, p. 7, No. 3a]

Open competition for funding from all sources: grants, contracts, cooperative agreements, and centers should take place.

Current Status

In all cases of NIH funding of AIDS and non-AIDS research, grant and contract applications are peer reviewed and awards are made based almost entirely on the results of the peer-review process thus ensuring open competition from all sources.

Most ICDs, including NIAID, NCI, NIDA, NIMH, NICHD, and NHLBI, will continue to build investigator-initiated research through R01s and PAs in lieu of RFAs and the selective pay mechanism. This policy appeals to applicants, who gain all the benefits of investigator-initiated research, including multiple receipt dates, multiple funding mechanisms, review by the DRG study sections, and a commitment to fund research in the stated area. The use of PAs also ensures open competition and comparable criteria for review and funding.

In response to the call to minimize the resources allocated in the absence of peer review, NCI has reduced its expenditures on many AIDS contracts and modified contracting procedures.

Future Actions

NIH will continue to strive to ensure that open competition and comparable criteria for review and funding are applied.

In addition, please refer to the NIH response to Recommendations 2–5.

Recommendation 190 [Etiology and Pathogenesis ARP Report, p. 7, No. 3b]

OAR should apply comparable NIH-wide criteria in evaluations of intramural and extramural research by the quality of science and the qualifications and productivity of the scientists and by the focus and potential impact on AIDS.

Recommendation 191 [Etiology and Pathogenesis ARP Report, p. 7, No. 3c]

These evaluations should be recurring regular reviews of all programs (extramural and intramural) with NIH funding by reviewing bodies with a majority of non-Government scientists.

Current Status

NIH agrees with the Panel that it is imperative to fund high-quality, meritorious intramural and extramural AIDS research programs.

OAR has a Congressional mandate to evaluate the AIDS research activities of each of the ICDs as well as provide for the periodic reevaluation of such activities. OAR's commitment to such evaluations is exemplified by the establishment of the highly productive NIH AIDS Research Program Evaluation Task Force with representatives from academia, industry, and community groups.

The responsibility for reviewing specific grant or contract applications is within the purview of either the DRG or ICD advisory bodies. All decisions regarding funding of research projects, both intramural and extramural, are based on the peer-review system. The review of all investigators involves both prospective and retrospective elements to varying degrees. Reviews of grant applications are typically considered prospective, although renewal is a partially retrospective process. Review of intramural projects is primarily retrospective. All these processes involve *ad hoc* reviewers and established panels of non-Government reviewers (DRG for extramural and Board of Scientific Counselors for intramural). It is through the balance of peer review and ICD review of programmatic relevance that decisions regarding funding of research projects are reached.

In 1994, NIH underwent an extensive review of its intramural research program by an external advisory committee cochaired by Drs. Paul Marks and Gail Cassell. Consistent with this committee's recommendations on the intramural review process, each independent scientist within a laboratory is reviewed every 4 years by a Board of Scientific Counselors, and the nature of the evaluation is mainly retrospective. The primary focus of this review is scientific excellence of the investigators. This review also incorporates evaluations of candidates recommended for tenure, overall staffing levels of the laboratory, space assignments, and budget for supplies, services, and equipment.

OAR believes that, even though intramural and extramural programs are reviewed by somewhat different processes, comparable levels of scientific excellence in both programs are expected and achieved.

Future Actions

NIH will strive to work with DRG in order to improve the quality and flexibility of the extramural review process and provide a linkage between review and strategic priorities outlined in the Plan. As a result of the Marks-Cassell report, the intramural review process has already been enhanced in all ICDs through increased rigor and comprehensiveness.

Recommendation 192 [Etiology and Pathogenesis ARP Report, p. 7, No. 3d]

Peer review should be improved.

- *The paramount consideration in constituting study sections and other reviewing bodies is scientific expertise, as determined by a previous record of scientific accomplishments, productivity, and knowledge of the field relevant to the review. Possible mechanisms to ensure high-quality reviews responsive to the changing scientific issues include working*

with learned societies to identify distinguished scientists with a broad range of expertise to serve on study sections, using voting ad hoc *members freely, and exercising flexibility on diversity and term limits for study sections.*

- *The review of senior investigators should be largely by merit or recent track record; review of junior or new investigators to AIDS research should be based on the research proposal.*

Current Status

NIH strongly endorses these recommendations concerning study sections and is taking active steps to implement them. DRG already is developing plans to work more closely with ICD staff and scientific societies to identify and use highly qualified reviewers as members of the initial review groups that review AIDS-related research grant applications, including SBIR grant applications.

In addition, recent changes in NIH policy have increased the flexibility for SRAs in recruiting the most highly qualified reviewers. A key change is the ability to have two members from the same institution. The prior restriction was prohibitive as many of the most distinguished scientists in this field reside at a relatively limited number of institutions. An additional change is that *ad hoc* reviewers (now termed temporary members) are permitted to vote at study section meetings, effectively increasing the flexibility in developing the review groups.

Currently, both the investigator's track record and the quality of his or her research proposal are considered within existing review criteria, and individual reviewers may legitimately place different weights on the various criteria for different applications. DRG proposes that the review process is best served by allowing flexibility in applying such criteria.

Future Actions

OAR and ICDs will continue to work with DRG to ensure that the review process is of high quality, flexible, and responsive to evolving scientific needs.

Recommendation 193 [Etiology and Pathogenesis ARP Report, p. 8, No. 3c]

The research focus on AIDS should be improved.

The DRG and study sections need to be better informed of OAR scientific priorities and need to view the relevance of a proposal to these priorities as an important criterion for funding. (Earlier recommendations in this document suggested mechanisms to enhance communication between study sections and programs.)

Current Status

NIH recognizes the paramount importance of developing a grant portfolio that is responsive to the evolving scientific priorities of the HIV/AIDS field. This process can be enhanced by an informal linkage between the review process and scientific priorities outlined in the NIH Plan for HIV-Related Research. DRG continues to support the principle of separation of scientific review from program prioritization. However, both initial review group members and ICD program staff and advisors would benefit from a stronger interaction based on common scientific goals. NIH has already started to work with DRG and OAR to develop mechanisms to enhance communication and encourage mutual awareness.

Proposed mechanisms include participation of scientific review administrators of AIDS study sections on the OAR Coordinating Committees responsible for the initial development of the annual NIH Plan for HIV-Related Research. In addition, the chair of each study section should be involved in the workshop meetings where non-Government scientists are asked to review the draft Plan and establish research priorities within the Plan. While it will be important for these study section members to be aware of the independence and separation of their programmatic and review responsibilities, it would not be inappropriate for them to brief their respective study sections on the scientific priorities and specific strategies outlined in the annual Plan at the outset of study section meetings or at a special session the evening before the meeting.

Future Actions

OAR will request DRG nominations of SRAs who would assist the OAR Coordinating Committees in the development of the annual NIH Plan for HIV-Related Research.

In addition, supplemental guidance in the PHS 398 application kit is being considered for grant applicants that would explicitly request that they explain how their proposed study relates to the scientific objectives and strategies of the annual Plan. Study section members also can be instructed to express any concerns about the AIDS relevance of an application in an administrative note to ICD staff.

In addition, please refer to the NIH responses to Recommendations 2 and 6.

Recommendation 194 [Etiology and Pathogenesis ARP Report, p. 8]

The Panel endorses changes in DRG recommended in the Cassman Report, which call for a peer-review oversight group (PROG) and peer review conducted by both DRG and ICDs, as appropriate. A body similar to PROG should be established for intramural research.

Please refer to the NIH response to Recommendation 190.

Recommendation 195 [Etiology and Pathogenesis ARP Report, p. 8]

OAR should have separate and parallel input to the final evaluation and ranking of review panels. For grants that remain classified as AIDS/AIDS-related following council review, funding decisions should be made by the Institute Director in consultation with the Director of OAR.

Current Status

NIH does not concur with the recommendation that OAR should have separate and parallel input into the final evaluation and ranking of grant applications by review panels or that funding decisions on AIDS-related grants by ICD Directors should be made in consultation with the OAR Director. The proposed alteration to require consultation of the ICD Director with the OAR Director is neither warranted nor necessary. The peer-review process serves as the cornerstone of NIH and its support of biomedical and behavioral research. This process represents a highly successful mechanism to review grant applications. NIH does, however, concur with other Task Force recommendations that propose further strengthening of the peer-review process.

Similarly, NIH takes the position that the determination of funding decisions for AIDS-related grants has and should continue to be the responsibility of the ICD Directors with advice and guidance from their advisory councils.

Please refer to the NIH responses to Recommendations 2 and 6.

Recommendation 196 [Etiology and Pathogenesis ARP Report, p. 8, No. 4]

Formulate and implement mechanisms to increase access to and improve the use of critical resources such as RPRCs and central repositories.

Please refer to the NIH responses to Recommendations 36, 37, 39, and 42.

Recommendation 197 [Etiology and Pathogenesis ARP Report, p. 8, No. 4a]

Competition for AIDS research project funding by NCRR at RPRCs should be opened to all extramural investigators, rather than only to permanent Center staff.

Please refer to the NIH responses to Recommendations 36 and 37.

Recommendation 198 [Etiology and Pathogenesis ARP Report, p. 8, No. 4b]

The NCRR study sections that review the RPRCs should incorporate expertise in AIDS and ARR.

Please refer to the NIH response to Recommendation 38.

Recommendation 199 [Etiology and Pathogenesis ARP Report, p. 8, No. 4c]

There should also be open competition for all relevant animal cost-funding of DRG-reviewed grants through a regularly recurring RFA.

Please refer to the NIH response to Recommendation 39.

Recommendation 200 [Etiology and Pathogenesis ARP Report, p. 9, No. 4d]

In view of the limited utility of chimpanzees for studies of AIDS pathogenesis, resources currently set aside for breeding and maintaining chimpanzees would be better used by NCRR for openly competed studies in macaques.

Current Status

In 1985, NIH determined, with the best information available at the time, that the chimpanzee would be the most appropriate model for AIDS vaccine research and development. Since the chimpanzee was an endangered species and importation was no longer possible, NCRR was instructed to use funds targeted for AIDS research to establish and maintain breeding colonies of this animal in anticipation of a demand for this species. The breeding colonies were successful. However, the anticipated demand has not materialized, predominantly because of the prohibitive cost of using these animals, the limited availability of housing for HIV-infected animals, and the apparent inability of HIV-infected chimpanzees to develop clinical signs of AIDS. Whereas it is true that the funds invested in this resource might be spent better on other avenues of research, no other means of support currently are available for these uninfected animals. NIH is currently committed to use AIDS research funds to maintain these animals. Euthanasia is not an option. The colonies are maintained at zero population growth by using birth control measures.

Future Actions

NIH has commissioned the National Academy of Sciences to study the use and need of the chimpanzee for biomedical research and to make recommendations for current and future (unforeseen) needs for this model. The report of this study is anticipated in the spring of 1997.

There is still a possibility, although remote, that this model may prove useful for studies of HIV pathogenesis if additional chimpanzees display the AIDS pathogenesis from HIV infection that was recently reported in an individual chimpanzee. Separately, however, investigators will be encouraged to use chimpanzees, when appropriate, for AIDS-related research studies. Where possible, investigators will be encouraged to use chimpanzees that have already been infected with HIV but which are symptom-free. This can be attained with modest incremental costs for research, since the per diem costs for these animals are already supported through endowment funds by NIH or other sources. This effort can be coordinated with the assistance of the OAR and the Interagency Animal Model Committee. However, careful planning and coordination of this effort is necessary.

NCRR plans to consolidate the uninfected chimpanzees at only two or three of the current five breeding sites for chimpanzee maintenance in an effort to decrease costs.

Recommendation 201 [Etiology and Pathogenesis ARP Report, p. 9, No. 4e]

OAR, in conjunction with the ICDs and extramural scientific community, should establish NIH-wide guidelines for access to clinical samples.

- *The type and frequency of samples collected should be appropriate to the investigation. This is a moving target that will require an explicit mechanism to ensure interaction between investigators, clinicians, and those responsible for the repository to decide what should be collected and priorities for distribution.*
- *Qualified investigators must have better access to samples. Guidelines currently being developed, e.g., at NIAID, should convey a sense of public ownership and should separate collection of samples from access to them by all qualified investigators. The sample repository should be seen as an opportunity to link basic and clinical investigators in collaborative studies.*

Please refer to the NIH response to Recommendation 42.

Recommendation 202 [Etiology and Pathogenesis ARP Report, p. 9, No. 5]

Define and focus the scientific portfolio of AIDS and AIDS-related research and associated program resources.

Please refer to the NIH response to Recommendation 44.

Recommendation 203 [Etiology and Pathogenesis ARP Report, p. 9, No. 5a]

The NIH and OAR should develop a new AIDS information system that lists grant titles and numbers, investigators' names and institutions, dollar amounts, funding ICDs, and

abstracts; is searchable by these parameters and by topic area (e.g., MESH headings); lists publications stemming from the research; can be applied equally to all NIH-funded AIDS research, both intramural and extramural; and is user-friendly and accessible to all those involved in the evaluation of NIH-funded AIDS research.

Please refer to the NIH response to Recommendation 43.

Recommendation 204 [Etiology and Pathogenesis ARP Report, p. 10, No. 5b]

Establish an evolving mechanism to define ARR through a conjoint effort of the ICDs and OAR, with involvement of the extramural research community. This definition should be broad but rigorous, consistent across ICDs, and updated annually. An explicit defensible rationale to define ARR should be linked to scientific issues and strategies and should be redefined as scientific progress reveals new areas of relevance. Research proposals should be predesignated by the principal investigator (PI) as AIDS or ARR and reviewed by appropriate panels that include OAR staff.

Please refer to the NIH response to Recommendation 44.

Recommendation 205 [Etiology and Pathogenesis ARP Report, p. 10, No. 6]

Maintain a strong OAR.

Current Status

NIH is committed to maintaining a strong OAR as mandated by the 1993 NIH Revitalization Act.

Future Actions

The NIH Director and ICD Directors have and will continue to vigorously support OAR in its planning, budgeting, coordinating, and evaluation responsibilities.

Recommendation 206 [Etiology and Pathogenesis ARP Report, p. 10, No. 6a]

OAR should set the scientific agenda and priorities in a collaborative effort with the directors of the ICDs, coordinating committees, working groups, councils and advisory bodies, non-Government researchers, and community representatives. To better communicate scientific priorities and funding, relevant study section chairs should be included in the process of setting the scientific agenda.

Please refer to the NIH response to Recommendation 2.

Recommendation 207 [Etiology and Pathogenesis ARP Report, p. 10, no. 6b]

OAR should align programs and resources by having and exercising fiduciary control over all NIH AIDS programs (not only the control over new and competing funds that were assigned to OAR in the NIH Revitalization Act of 1993), including intramural research, contracts, and cooperative agreements. Without central fiscal authority to fund scientific priorities, the identification of these priorities becomes a meaningless exercise.

Current Status

The NIH Revitalization Act of 1993 provides the legislative authority for OAR. The legislation requires the Director of OAR to "plan, coordinate, and evaluate AIDS research and other activities conducted or supported by the agencies of the National Institutes of Health." The Director is further required to carry out these responsibilities "in consultation with the heads of the agencies of NIH, with the advisory councils of the agencies" and with the OARAC. The legislation requires the development for an annual research plan, which sets scientific priorities and provides for research that is both conducted by and supported by NIH. The Plan "serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of scientific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan." The law requires that all AIDS research should be carried out in accordance with the Plan.

Future Actions

NIH believes that the existing authorities provide a suitable mechanism to plan, coordinate, and implement the scientific priorities in AIDS research through the important interactions between OAR and the ICDs. The ICDs work collaboratively with OAR in the planning and evaluation processes, but it is the role of the ICDs to implement the scientific agenda. The ICDs have highly qualified staff dedicated to this purpose, and they have the legal responsibility to allocate research funds through the various funding mechanisms.

Recommendation 208 [Etiology and Pathogenesis ARP Report, p. 11, No. 6c]

OAR and the ICDs should continue to regularly and systematically solicit advice from leading Government and non-Government scientists in the formulation and plans for pathogenesis research.

Please refer to the NIH responses to Recommendations 44 and 124.

Recommendation 209 [Etiology and Pathogenesis ARP Report, p. 33]

With a certainty that animal models will continue to be important in the future for studying AIDS pathogenesis, continued support for animal model research is warranted. A broadly based portfolio that supports research into natural lentiviral infections of many species is encouraged. For focused AIDS-specific questions, emphasis should be placed on nonhuman primate models in which AIDS occurs. Murine systems will be useful for restricted purposes. Funding mechanisms that bypass true, open competition for funds should be eliminated. If an Institute is not in a position to oversee open competition for the funds, these funds should be dispensed to other Institutes.

Please refer to the NIH responses to Recommendations 231 and 233.

Recommendation 210 [Etiology and Pathogenesis ARP Report, p. 36]

OAR should coordinate all efforts directed at neuro-AIDS across the NIH in all intramural and extramural programs, and by all mechanisms, to align the research programs with the scientific priorities. The RFA on the blood brain barrier and neuro-AIDS jointly issued by NIMH and NINDS and workshops on neuro-AIDS cosponsored by NIMH, NINDS, and NIAID provide recent and past examples of fruitful cooperative ventures and a paradigm for the future, for both research and training.

Current Status

NIH recognizes the critical need to align neuro-AIDS research programs with the scientific priorities and to improve trans-NIH coordination of related activities.

In an effort to more effectively align NIH research programs with scientific priorities in the neuropathogenesis area, NIMH, NINDS, NIDA, and NICHD have jointly issued a PA in FY 1997 concerning HIV infection of the CNS. The objective of this cooperative effort is to foster investigations that will provide the foundation for the rapid development of therapeutic interventions to prevent and treat the effects of HIV on the CNS. The research topics identified in the PA reflect those considered to be the most pressing scientific priorities by the ICDs, OAR, the Etiology and Pathogenesis Area Review Panel, and other outside experts.

Future Actions

To improve and facilitate the future coordination of cross-Institute efforts and to more effectively identify and implement key neuro-AIDS initiatives, NIH will establish a working group consisting of members from the ICDs with neuropathogenesis research programs and a liaison from OAR. The group will prioritize and develop an inter-ICD plan for implementing neuro-AIDS research initiatives based on the strategic plan. This approach will allow various research programs to coordinate more effectively their efforts to address scientific priorities. This strategy should result in minimizing programmatic overlap and fostering synergies among the various research programs.

Recommendation 211 [Etiology and Pathogenesis ARP Report, p. 36]

Substantial support for research the Subpanel views as highly relevant and likely to impact greatly on neuro-AIDS can be generated by redirecting and refocusing resources, using existing mechanisms that involve OAR, the NIH, and non-Government scientific communities. The coordinating committees and annual OAR workshops define and redefine scientific priorities and AAR. These definitions should be utilized to align programs and resources and to replace current practices in research that is tangentially related to neuro-AIDS or apparently unrelated but important to neuroscience and that might eventually prove related (such as work on opiate receptors) is classified as ARR. This work should be supported on its own merits and not as ARR. Similarly, practices of arbitrarily assigning funding as neuro-AIDS, e.g., in ACTUs, should be discontinued in favor of rigorous and explicit rationales for designating funding as neuro-AIDS.

Current Status

The field now described as neuro-AIDS began as a clinical designation of HIV-infected individuals with neurological and neurobehavioral impairments. In recent years, neuro-AIDS has evolved into an area with well-defined pathological, neurological, and neuropsychological characteristics and study parameters.

Initially, studies were directed toward understanding fundamental nervous system involvement in AIDS. These studies were typically descriptive. Currently, investigations are directed more toward elucidating the mechanisms of HIV damage in the nervous system. As a result, the roles of viral components, inflammatory responses, cytokines, and chemokines in the complex manifestations of neuro-AIDS have become clearer. Consequently, findings from basic and clinical investigations now guide work in the field serving to focus studies on specific areas. ICDs with neuropathogenesis research programs contribute to the definitions of neuro-AIDS research contained in the goals, objectives, and strategies outlined in the annual NIH Plan for HIV-Related Research. The identification of fundamental areas of basic research that may yield insights that are necessary to advance an understanding of HIV neuropathogenesis are also included in these strategic planning discussions. The agreed-upon strategies form the basis for program initiatives and the distribution of resources.

Future Actions

In an effort to improve and facilitate the future coordination of cross-Institute efforts to identify and implement key neuro-AIDS initiatives, NIH will establish a working group composed of representatives from each of the various ICDs with neuropathogenesis research programs and a liaison from OAR to prioritize and develop inter-ICD plans for implementing the neuro-AIDS research initiatives of the annual NIH Plan.

Recommendation 212 [Etiology and Pathogenesis ARP Report, p. 37]

> *Shared resources are critical to the success of understanding the pathogenesis of neuro-AIDS. These resources include the primate centers, designated centers for neuro-AIDS research, and tissue repositories essential for research with* in vivo *relevance. The Subpanel endorses the conclusions of a number of the Area Review Panels that access to the primate and transgenic murine models must be improved. The Subpanel also supports efforts to improve centralized systems to collect, catalog, and distribute reagents and tissue specimens and the involvement of the scientific community in determining the type and frequency of sample collection.*

Current Status

Many studies in neuro-AIDS research are dependent upon the utilization of postmortem tissue as well as the employment of appropriate animal models and tissue culture systems. NIH agrees with the Neuropathogenesis Subpanel Report, which contended that sharing of these valuable resources is critical to the success of understanding the pathogenesis of neuro-AIDS. The complexity and multidisciplinary nature of this research require investigators to have access to information that will facilitate collaborative exchanges and maximize the use of these resources.

Future Actions

The implementation of a coordinated, inter-ICD effort to facilitate the voluntary exchange of information and materials from research organizations that collect, store, and distribute nervous system specimens will be a priority topic of consideration by the neuro-AIDS working group that will soon be established. Topics to be discussed will include (1) the establishment of a national electronic/hard copy registry of HIV-related neurological specimens that are made available to the research community without personal identifiers to ensure confidentiality by research organizations, such as the Neurological AIDS Research Consortium; (2) the establishment of standardized procedures for the collection and storage of postmortem HIV/CNS specimens; and (3) the support of efforts to increase antemortem consents for autopsies and the donation of resulting neurological tissue for HIV/CNS research. A similar electronic database would also be established for the cataloging of information available from various animal and tissue culture system studies pursuing neuro-AIDS research.

In addition, please refer to NIH response to Recommendation 42.

Vaccine Research and Development Area Review Panel Recommendations

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Recommendation 213 [Vaccine Research and Development ARP Report, p. 3]

Create an IRG that would be dedicated to broad aspects of vaccine research, including both HIV and other pathogens.

Please refer to the NIH response to Recommendation 8.

Recommendation 214 [Vaccine Research and Development ARP Report, p. 3]

Continue NIH/NIAID efforts to encourage and solicit the research community to submit applications in vaccine biology and immunology.

Current Status

The ongoing efforts of NIH through NIAID to actively solicit applications in vaccine biology and immunology were recognized and supported by the Vaccine Research and Development Area Review Panel. Where appropriate, other ICDs will convey this interest to members of their respective research communities.

Future Actions

OAR will continue to encourage NICHD, the National Institute of Dental Research (NIDR), NCI, and particularly NCRR to support areas of research relevant to vaccine biology and immunology, consistent with their ICD mission, through investigator-initiated grants and centers mechanisms.

Recommendation 215 [Vaccine Research and Development ARP Report, p. 3]

Selectively target vaccine-related research areas for special consideration during review and funding.

Current Status

Applications for NIH funding are evaluated for scientific merit and importance to AIDS vaccine research by the AIDS and Related Research study sections. Staff of the DRG and several ICDs are aware that it has been difficult to achieve appropriate levels of investigator-initiated funding in this highly pragmatic area of research. It has been the role of ICD program staff to target selectively those applications of high relevance to vaccine research and bring them to the attention of the ICD advisory councils for special consideration. Council members as well as IRGs continuously should be made aware of the important public health need for enhanced funding in the area of vaccine research.

Future Actions

DRG and OAR will explore avenues to ensure that members of IRGs are informed of the importance that NIH, in line with recommendations from advisory and program review groups such as this, has placed on the pragmatic aspects of vaccine research as well as the understanding of basic mechanisms and principles of vaccine design and development.

Please refer to the NIH response to Recommendation 225.

Recommendation 216 [Vaccine Research and Development ARP Report, p. 3]

Increase the access of basic research scientists, who are interested in HIV interactions with the human immune system, to clinical materials emerging from studies within existing networks such as the Multicenter AIDS Cohort Study (MACS), the AIDS Vaccine Evaluation Group (AVEG), and the HIV Network for Efficacy Trials (HIVNET) and from certain animal model studies.

Please refer to the NIH response to Recommendation 42 Part B.

Recommendation 217 [Vaccine Research and Development ARP Report, p. 3]

The Panel specifically supports and commends the recent establishment of a Vaccine Design Focus Group by NIAID. This group is composed of intramural and extramural investigators from both academia and industry who have direct experience in vaccine design and immunogenicity and are empowered to make appropriate priority choices.

Recommendation 218 [Vaccine Research and Development ARP Report, p. 4]

The charge of this group should be expanded to an NIH-wide effort to: (1) understand the early step in viral infection and pathogenesis in the host, (2) evaluate candidate vaccines in a systematic manner that will allow promising approaches to be identified, (3) determine correlates of immunity, and (4) establish primary (prevention of infection) and secondary (attenuation of infection such that disease is prevented and transmission is curtailed) vaccine goals. Another critical role of the expanded Vaccine Design Focus Group should be to seek out and evaluate new vaccine candidates, so that it can recommend the most promising concepts for clinical testing by the AIDS Vaccine Evaluation Group (AVEG) (see below).

Current Status and Future Actions

The Vaccine Design and Evaluation Group (VDEG) has provided invaluable guidance to NIAID staff and the scientific community on scientific priorities and the use of valuable and limited animal resources. The role of this group will continue unchanged until the AVRC, formed in February

1997, determines the need for the VDEG including its possible expansion, responsibilities, and operational functions.

Recommendation 219 [Vaccine Research and Development ARP Report, p. 4]

AVEG should work closely with the Vaccine Design Focus Group to encourage the preclinical development of promising vaccine candidates that are suitable for clinical evaluation in Phase I and II studies as well as those that might prove worthy of evaluation for efficacy.

Guidelines should be established for the advancement of a vaccine product to efficacy trials sponsored by the NIH. Although the precise criteria might vary with the nature of the concept under evaluation, a product ideally should be shown to induce humoral and cellular immunity that is broad, durable, and likely to provide a significant barrier to natural HIV infection. If and when appropriate animal models become available, demonstration of protection in the preclinical evaluation with such models should support the entry of a vaccine into efficacy trials.

Current Status

NIAID agrees with the Panel that a strong and dynamic working relationship between the VDEG and the AVEG is important. The AVEG is very proactive in seeking out information about candidates in preclinical development.

In its December 1995 document entitled "NIAID HIV Vaccine Research and Development, Strategy and Opportunity," NIAID describes the general principles it will use in establishing guidelines for each vaccine product/concept before efficacy studies are initiated. Specific guidelines for each vaccine concept will be outlined in the development plans, which are constructed in concert with the vaccine manufacturer, the VDEG, and AVEG and HIVNET investigators. NIAID anticipates that the AVRC will also be involved in this process.

Future Actions

NIAID will continue to encourage and facilitate ongoing communication between the preclinical groups and the AVEG.

In addition, please refer to the NIH response to Recommendation 218.

Recommendation 220 [Vaccine Research and Development ARP Report, p. 5]

AVEG also should invest more effort on in-depth comprehensive assessments of human immune responses to HIV antigens. Greater emphasis should be placed on the laboratory analysis of immune responses in vaccinees, even if this necessitates the study of many fewer individuals with any one vaccine candidate. Among immune system

parameters that should be evaluated in more detail are the generation, function, and specificity of cytotoxic T lymphocytes (CTLs); the relevance of neutralizing and nonneutralizing antibodies; the importance of Th1 and Th2 subsets of helper T cells; the targeting of immune cells to mucosal sites; the sensitivity to infection and function of antigen-presenting cells (particularly dendritic cells); and the roles of Type 1 versus Type 2 cytokines in specific and nonspecific immunity to viral infection. The participation of non-AVEG investigators in such studies is essential and should be encouraged.

Current Status

NIAID and the AVEG investigators agree that comprehensive studies of the immune responses to HIV antigens are important and should be expanded. In fact, studies of CTL generation and targeting of immune cells (such as CTLs) to mucosal sites have been peer reviewed and are being conducted by AVEG and outside investigators. OAR has generously provided supplemental funds over the last several years to expand these studies.

The AVEG has an intensive protocol for followup of vaccinees who become HIV-infected. These individuals have been extensively studied in a collaboration between the AVEG and the investigators for the Correlates of HIV Immune Protection contract. Many of the scientific questions raised by the review panel also are being addressed by investigators collaborating with the natural history cohorts (e.g., MACS, WITS, and WIHS) and/or investigator-initiated research associated with NIAID clinical trials and natural history networks of HIV-infected individuals.

Future Actions

NIAID will continue to support intensive study of the immune responses of vaccinees to HIV antigens. More detailed studies will continue to be performed on subsets of volunteers. Scientific advances will be reflected in the priorities for these studies.

Recommendation 221 [Vaccine Research and Development ARP Report, p. 5]

NIAID should rapidly reassess the status of the HIVNET program. It is likely that few expanded (Phase II or efficacy) vaccine trials will be conducted within the next 5 years; thus, a careful reevaluation of the size and nature of HIVNET programs is now needed. The seronegative cohorts that have been established for determination of seroincidence can and should be used to evaluate biomedical and/or behavioral strategies designed for reduction in HIV transmission, as has been proposed by HIVNET. If appropriately sampled, these and future cohorts also would be of value for studies of primary HIV infection and pathogenesis, and studies of early treatment of acute infection. However, because the principal mission of HIVNET has been vaccine preparedness, it is not obvious that HIVNET has the intrinsic expertise or infrastructure to move effectively beyond its original mission. This raises the question of where and how such expanded

studies are best undertaken. NIAID should promptly compile a comprehensive research plan for the HIVNET effort that addresses these issues. This plan should be reviewed by a panel of experts in behavioral, epidemiologic, prevention, and pathogenesis research. The Panel also urges NIAID to prepare an overall funding strategy for HIVNET that is congruent with plans for vaccine development, and that should be reviewed by the OAR. Finally, NIAID should strengthen the ties between AVEG and HIVNET so that each group can benefit from the expertise of the other.

Current Status

A scientific plan was developed in 1996 by HIVNET investigators and NIH staff. This plan outlined scientific priorities taking into account the likely availability of vaccines for expanded Phase II or efficacy trials within the next few years. These plans include the conduct of a joint vaccine trial by AVEG and selected HIVNET sites. In June 1996, NIAID and OAR convened a multidisciplinary group of experts to conduct a review of the HIVNET organization, governance, research, and funding.

With respect to the points raised in this recommendation, the external review made the following conclusions:

- HIVNET must continue to maintain a strong multidisciplinary approach to maintain or develop its capacity for evaluating both vaccine and nonvaccine interventions.

- In addition to the ongoing program of research related directly to vaccine efficacy trials, HIVNET's domestic and international cohorts provide a valuable resource for evaluating other biomedical and behavioral interventions for preventing sexual, parenteral, and perinatal transmission of HIV. Inter-Institute/agency collaboration for microbicidal and perinatal transmission studies and OAR-based coordination for behavioral studies are essential for defining the scope and setting priorities for these non-vaccine-based activities.

- For non-vaccine-based activities, prioritization and implementation plans should include clearly articulated guidelines for the choice of product or interventions. For microbicides and perinatal transmission research, these guidelines should include the potential global availability of products, biological endpoints, and individual rather than community intervention strategies. Behavioral research should focus on descriptive or methodological studies essential for the conduct of vaccine trials. When promising behavioral interventions have been identified as suitable for testing in the HIVNET, they should be tested using HIV infection as the trial outcome measure.

Future Actions

NIAID and AVEG and HIVNET investigators agree on the need for strengthening their ties. They are proceeding with plans for a jointly conducted Phase II vaccine trial. The first joint

AVEG/HIVNET meeting took place in November 1996. NIAID will continue to facilitate and promote stronger interactions.

In addition, please refer to the NIH response to Recommendation 260.

Recommendation 222 [Vaccine Research and Development ARP Report, p. 6]

The Panel found NIAID's extramural vaccine efforts to be well-integrated; however, the vaccine-related activities at the NCI, NIDR, and the NCRR appear to be critically lacking in oversight and coordination. The entire HIV vaccine effort of NIH would best be coordinated by the OAR with centralization in a single ICD, such as NIAID, and with appropriate linkages to other ICDs. Establishment of such a program requires that a strong, effective, and visible leadership structure be created that includes non-Government experts who have had extensive experience in vaccine research and development. Such an organizational structure will also enable OAR to address the problems related to a balanced allocation of annual resources (and discretionary resources) where they are most needed for AIDS Vaccine Research and Development.

Current Status

Basic vaccine research efforts are largely funded through RPGs or investigator-initiated intramural research projects. Most of the extramural targeted research or preclinical studies are now coordinated by NIAID through its VDEG, a group of investigators from academic institutions with some representatives from industry and relevant NIH intramural programs.

AVEG, NIAID's extramural consortium of nine academic institutions and a data center, conducts the majority of HIV vaccine clinical trials funded by NIH (25 of 27 NIH-sponsored trials in HIV-uninfected adults). The AVEG Executive Group has made it a priority to coordinate these trials with NIH intramural scientists and other investigators, including trials funded by private manufacturers or non-U.S. governments.

Future Actions

NIH agrees with the Panel on the need for improved coordination of AIDS vaccine studies to avoid duplication and ensure that each NIH trial is focused on a specific scientific question. Because basic and preclinical vaccine activities continue to include other ICDs, it is anticipated that AVRC will be invaluable in coordinating these efforts.

In addition, please refer to the NIH response to Recommendation 15.

Recommendation 223 [Vaccine Research and Development ARP Report, p. 22]

NIH should increase total funds allocated to basic research in support of vaccine design and development. In particular, basic research on immune responses in humans and macaques should be targeted as an area of the highest priority.

Current Status

This recommendation is in part repetitive of **Recommendations 12, 19, and 20** to increase resources to basic research and also overlaps with the sentiments to raise the priority of vaccine research expressed in **Recommendation 15.**

The NIH recognizes the urgent need to increase the total funds allocated to vaccine design and development. In complementing the responses to the indicated recommendations, it is necessary to note some information that was not available to the NIH AIDS Research Program Evaluation Task Force and the Area Review Panels. A substantial investment in the areas of human and nonhuman primate immunological research has already been made (only a small portion of this is classified as AIDS-related research). Extensive effort in NIAID is going into basic studies of Class I-restricted CTL, including funding for studies in humans and macaques and provision of reagents to the general research community.

To facilitate implementation of this recommendation, the OAR worked with the ICDs to fund several new grants and supplemented existing grants in basic and vaccine-related immunology of humans and nonhuman primates in FY 1996.

Future Actions

The NIH agrees that basic research on immune responses in humans and nonhuman primates continues to be invaluable in facilitating improved HIV vaccine design and development. National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIDCD, NIDR, NIDDK, and Office of Research on Women's Health (ORWH) have expressed interest in joining NIAID in a PA in FY 1997 for research on mucosal immunity and its regulation. NICHD sponsored a meeting on sexual transmission of HIV in February 1997. NIDR will sponsor a meeting in September 1997 to highlight advances in various aspects of mucosal immunity to HIV as well as pathogenesis, vaccines, and HIV transmission. In addition, advances in human and nonhuman primate immunology of HIV vaccines were presented at the NCVDG meeting in May 1997.

Recommendation 224 [Vaccine Research and Development ARP Report, p. 22]

The Division of Research Grants (DRG) should develop a newly configured separate study section for vaccine-related research.

The obvious solution to address a deficiency in a specific area of research is a separate study section for that area. Separate, ad hoc *study sections, such as those that have been constituted for review of RFAs, do not have continuity built into their structure and thus fail to address the long-term practical issues associated with flexibility for consideration of newly emerging concepts and reevaluation of revised applications. A continuing study section on vaccines would require a very broad expertise in many related areas.*

Please refer to the NIH response to Recommendation 8.

Recommendation 225 [Vaccine Research and Development ARP Report, p. 22]

NIH should allocate specific funding for vaccine-related research to stimulate the fundamental research needed in immunology and vaccine design.

Even if a new permanent Vaccine Study Section could be established in the near future, the problem requires an immediate intervention. The ICDs, in collaboration with OAR, should be encouraged to allocate a defined amount of funding in each fiscal year for targeted areas of basic research that are specified as high priority for vaccine development. All grant applications that are received would be examined for their relevance to these areas and would be designated for special consideration by DRG staff and the chair of the study section. The study section members reviewing the application might be requested to give the grants a "relevance score" from 1 to 5 based on their perception of the application's relevance to the targeted areas. The study section would be informed that these designated applications would be funded from the separate allocation of funds, because this research was a national priority. The payline for these applications might be much higher than the payline for all other applications reviewed by that study section. Care should be taken by DRG, ICD, and OAR staff to recognize artificial maneuvers to utilize "buzzwords" in the abstracts or Specific Aims that trigger designation for targeted review. Placing applications in this separate category should be done thoughtfully and fairly, and should also involve input from the chair of the study section at the time of the review.

The Immunobiology Study Section or the AIDS-related Research-A (ARRA) study section might be an appropriate study section for these grants; if necessary, a few new members could be added with specific expertise and interest in vaccines.

Current Status

The issues raised in this recommendation overlap those raised in **Recommendation 197.**

Solicitation of applications: Solicitations of applications are usually sought through RFAs or through PAs. PAs may have an advantage over RFAs depending on the scope of the research. Because of the limited life span of an RFA, there is no provision for reviewing amended or renewal applications. Investigator-initiated applications submitted in response to PAs may be

broader in scope and concepts than applications received in response to RFAs, which usually request applications in highly targeted areas of research.

Review of applications for scientific merit and relevance: At NIH, the assessment of the program relevance of a research application has traditionally been the role of ICD program staff and ICD advisory councils of nongovernmental scientists.

Future Actions

Study section composition: To review vaccine-oriented applications in the current chartered study section may complicate the evaluation process if vaccine research applications receive special treatment or are funded from a separate pool of money. It is, therefore, suggested that a SEP be established by DRG to review applications referred as vaccine-related. Members of this SEP will be recruited from academic and nonprofit research institutions, industry, and the intramural community. With the establishment of a SEP, there is no compelling reason to set up a new chartered study section to review vaccine-oriented applications in order to achieve appropriate reviews for this area of research. Furthermore, the SEP can be drawn immediately from already existing IRGs with additional expertise added as necessary.

NIAID and NCRR have designated funds within their planning budgets to accommodate responses to PAs and RFAs in vaccine-related research that meet appropriate standards of peer review, either through regular DRG assignment and review in AIDS-related Research-A (ARRA) study sections or through SEPs. Most complex mechanisms such as U01, U19, and P01 grants will continue to be handled in ICD-specific IRGs.

The suggested recommendation to refer grants to a subpanel of ARRA will be considered for FY 1997. Further changes will await the decision of the newly appointed head of DRG.

Efforts to acquaint both study section members and potential applicants with the priority with which NIH views vaccine-related research will begin immediately. Distribution of the annual NIH Plan for HIV-Related Research, which has been formulated with extensive insight from extramural, intramural, and program staff scientists, will be completed by OAR with the cooperation of DRG and other ICDs. Selected study section members will be included in the planning process to encourage overall familiarity with the scope and priorities of this plan.

Recommendation 226 [Vaccine Research and Development ARP Report, p. 23]

> *All future research devoted to the development and analysis of vaccination strategies should involve forging more extensive collaborative links with cellular immunologists.*
>
> *This applies to both nonhuman primate and clinical human AIDS vaccine trials, and could enable a better understanding of the consequences of immunization. It is recognized that many of the leading immunologists in the United States have not been involved in AIDS vaccine research to any significant extent. The Panel felt that it is vital to develop ways to change this situation. A culture must be created that will lead to*

improving our understanding of immunogenicity to viral antigens. Thus the Panel strongly recommends development of funding mechanisms designed to attract creative young investigators and experienced immunologists to this complex and challenging area of research.

Current Status

This recommendation is directly related to the NIH responses to **Recommendations 11, 12, 19, and 20.** In addition, this recommendation overlaps **Recommendations 214 and 215.**

NIAID and OAR have funded a series of activities that will generate new reagents for studying T-cell responses to HIV antigens and make them available to the vaccine research community. The NIH agrees that further effort to encourage collaborative links focused on the immunology of nonhuman primate models is also warranted. In the past several years, new reagents and information have become available to enable the evaluation of specific immune responses generated in response to vaccines. Some of these new findings were presented in October 1996 at the 14th Annual Symposium on Nonhuman Primate Models for AIDS in Portland, Oregon.

Future Actions

In addition to ongoing efforts, NIAID and OAR will make a special effort at the next NCVDG meeting to highlight immunological studies in humans and nonhuman primates and any additional technical advances and to encourage investigators to share valuable reagents for cytokine and T-cell analyses.

Recommendation 227 [Vaccine Research and Development ARP Report, p. 23]

Clinical samples, from vaccine trials and relevant NIH-supported natural history cohorts, as well as viral stocks for experimental animal models, should be made more readily available to researchers, with appropriate research plans, outside the groups involved with the initial sample and data acquisition.

Please refer to the NIH response to Recommendation 42.

Recommendation 228 [Vaccine Research and Development ARP Report, p. 23]

Approval of these plans should fall within the purview of an independent committee, and not, as at present, solely under the control of the group which has collected the samples. The supply of materials available, and competing demands upon them, should be taken into account. The Panel noted the success of the NIAID AIDS Reference and Reagent

Program in providing virus stocks and other reagents obtained from clinical sites and basic researchers for distribution to the research community.

Please refer to the NIH responses to Recommendations 42 and 289.

Recommendation 229 [Vaccine Research and Development ARP Report, p. 23]

NIH should reevaluate the relative distribution of resources between clinical evaluation of current vaccine candidates and the development of new ones with potentially greater promise. Redundant funding for clinical trials of similar vaccine candidates should be eliminated in favor of new vaccine concepts. NIH should establish mechanisms for identifying novel approaches to vaccine development and rapidly testing their feasibility.

Current Status

NIH agrees with the Panel that redundant trials should not be supported. NIH does not believe that NIAID has funded "redundant" trials either within the AVEG or in the intramural program. While several vaccine trials may have utilized products from the same general class, each clinical trial has been designed to explore the immunogenicity and safety of individual vaccine types, formulations, doses, schedules, or routes of administration—either alone or in combination. Currently, intramural and extramural staff communicate regularly and meet with funded investigators to ensure that efforts are not being duplicated. The AVRC also will aid in the oversight of vaccine research efforts throughout NIH.

NIH recognizes the need to increase the number of new vaccine concepts to be evaluated. To that end, NIAID has recently published a PA to encourage investigator-initiated research at the beginning of the vaccine pipeline. NIAID also makes reagents and testing facilities available to the research community to foster development of novel vaccine approaches.

Future Actions

NIAID has released an RFA for funding in FY 1998 that will expand the NCVDG program and institute a program designed to bridge preclinical and early clinical development and pilot testing of novel vaccine concepts. These programs are being put into place to build on the current efforts to increase basic discovery and design of a variety of novel vaccine approaches. NIAID believes that these initiatives, from basic research through early clinical evaluations, will assist in the rapid translation of vaccine concepts to clinical candidates.

Recommendation 230 [Vaccine Research and Development ARP Report, p. 23]

NIAID and NCI research programs on HIV-1 genetic variation should be better coordinated, both within the NIH and with other agencies pursuing this problem, including the DoD, CDC, EEC, and WHO.

Although NIAID has been proactive in this regard, HIV genetic variation research programs of the newly created HIVNET are likely to duplicate other activities already supported by NIAID, including NIAID-sponsored work by the WHO (WHO AIDS research activities will be subsumed within a new United Nations structure, the UNAIDS Program, during 1996).

Current Status

NIAID is the lead ICD for research, analysis, and data management of HIV/AIDS genetic information. NIAID participates in the UNAIDS for worldwide genetic research and will continue to emphasize coordination with this organization. Over the past few years, relatively small projects either in intramural laboratories or funded in extramural research by NCI have been coordinated with NIAID and UNAIDS efforts.

Future Actions

Coordination of the international effort led by WHO/UNAIDS to study genetic variation and antigenic variation of HIV has been needed to conserve resources and provide as wide an information base as possible. NIH will continue to participate fully in the integrated international program. The Los Alamos HIV database supported by NIAID provides a critical tool for coordination and distribution of this information and will be continued. Staff scientists in NIAID continue to work with DoD scientists at Walter Reed Army Institute for Research (WRAIR) and CDC representatives to ensure timely incorporation of information into the database. HIVNET programs recently have been reviewed. Their focus has been and will continue to be the evaluation of both domestic and international potential vaccine trial sites, which includes the monitoring for emerging HIV-1 subtypes in those sites. HIVNET will provide specimens as needed to UNAIDS through the NIAID Genetic Variation Program. Collection of additional specimens can be arranged through the AITRP of FIC. Standard panels of diverse HIV-1 isolates already are available to the scientific community through the NIAID reagent program. An additional panel of international HIV-1 isolates has been selected in coordination with NIAID, WRAIR/DoD, and WHO/UNAIDS from several sources and will be prepared commercially for assay standards of non-B clade viruses.

In addition, please refer to the NIH response to Recommendation 17.

Recommendation 231 [Vaccine Research and Development ARP Report, p. 24]

A rationalization of the simian animal model field and a redistribution of funding for a significant fraction of the current animal models is imperative. The Subpanel recommends performance of fewer, but more detailed, studies, each using an increased number of animals.

A top-level, independent expert group (see the Targeted Vaccine Subpanel Report) should develop criteria for the continuation or expanded utilization of an animal model in vaccine research and determine which of the current models meet those criteria. Among the current simian models, there is a spectrum of viral virulence and consequent pathogenicity. Some virus strains in some animals replicate only to low levels, cause only limited disease, and tend to be relatively easy to protect against infection by immunization with SIV antigens. Conversely, other models replicate to high levels in vivo*, cause rapid disease, and are hard to protect against. The Panel felt that, in principle, it was important to retain one simian model at each end of the spectrum and perhaps one in the middle for larger comparative vaccine studies. When developing a new vaccine concept, it is advantageous to show that it confers protection under favorable conditions, yet a rigorous test of the concept is also important. The considered development and use of assays to measure virus load in plasma and tissues is essential for assessing the comparative worth of simian models and for determining the outcome of vaccine trials.*

Current Status

The NIH research community recognizes the value of identifying models suitable for comparative evaluation of vaccine approaches. However, the various models currently in use largely mirror the range of outcomes seen following human HIV exposure. The NIH will continue to rely on peer-reviewed, investigator-initiated research using animal models to evaluate the relative value of any one system in AIDS vaccine research. Until basic studies elucidate viral and host mechanisms that influence natural resistance, virulence, and immune protection, it would be premature to limit an investigator's flexibility. The NIH will strive to identify test systems in nonhuman primates that closely mirror the viral/host interactions in the human HIV response. In the interim, NIAID already has in place the VDEG that reviews progress of animal model research for vaccine development and proposes priorities for targeted vaccine research. In addition, the NCRR-funded RPRCs have an AIDS Coordinating Committee that reviews needs and use of nonhuman primates at the seven RPRCs.

Future Actions

It is anticipated that the AVRC will review the current NIAID VDEG in the context of these concerns and, on the basis of gaps identified, will either expand the VDEG to include representatives from other ICDs or arrange to have the different ICD groups report directly to the AVRC.

Recommendation 232 [Vaccine Research and Development ARP Report, p. 24]

NIH-supported basic vaccine research on the HIV-1/Chimpanzee model should focus almost exclusively on the development of a challenge strain that would replicate to high titers in these animals and cause disease.

The current stocks of virus that replicate poorly in chimpanzees have limited value, except for initial "proof of concept" studies.

Current Status

Vaccine testing in chimpanzees has been limited to assessment in a nondisease model. As such, chimpanzees have provided valuable insights into human immune responses but limited information about preventing pathogenic infection. The potential range of experiments has been expanded since the recent identification of several HIV-1 isolates that replicate to high titer in chimpanzees and the recent development of AIDS (complete with OIs) and/or profound CD4 T-cell loss in chimpanzees initially infected with HIV more than 10 years ago at the Yerkes RPRC. For the chimpanzee model to be more useful, challenge stocks able to infect chimpanzees by mucosal as well as intravenous routes are being developed, including some from HIV clades other than B. It is expected that this model will continue to be used in limited but well-designed experimentation. In addition to the ethical concerns about use of these animals, the current expense that is associated with long-term maintenance of these animals will be a deterrent to this research.

In the past several years, NIAID has funded research to assess the ability of clade B and non-clade-B HIV-1 isolates to replicate in chimpanzee cells and test mucosal challenge stocks for research in chimpanzees through grant and contract mechanisms. From FY 1994 through FY 1996, NIAID and OAR (FY 1994) funded research in intramural and extramural laboratories to develop and analyze a more virulent clade-B HIV isolate. In FY 1996, NCI funded the titration of a primary clade-B HIV (5016) stock for use in heterologous vaccine challenges.

Future Actions

Because most viral stocks have replicated poorly in the chimpanzee and have not caused disease, virulent strains must be propagated for additional research purposes. If defined needs exist, titered challenge stocks of these will be prepared or acquired and made available to vaccine researchers. Continued progress in development of new stocks of virus is essential in order to allow vaccine studies to evaluate protection against disease development within a reasonable time frame. In FY 1996, the investigators at the Yerkes RPRC were given supplemental funding by NCRR and NIAID to continue studies on a highly virulent strain of HIV from diseased chimpanzees. This award was, in part, for the development of a repository of this viral stock to be provided to the NIAID for distribution to other AIDS investigators. Experiments on the use of novel isolates in chimpanzees are being supported through investigator-initiated research. Funding to support vaccine challenge studies in chimpanzees using more virulent isolates and modeling human transmission of HIV will meet defined needs.

The AVRC, as part of its role in coordination of NIH HIV-AIDS targeted vaccine research, also will review information on isolates intended for expanded use in chimpanzees. The committee periodically forwards its suggestions for preparation of challenge stocks to the Interagency Animal Model Committee and to OAR or to relevant ICDs for funding action. NIH also will take under consideration the recommendations of the currently ongoing National Research Council review of the use and long-term maintenance of these animals.

Recommendation 233 [Vaccine Research and Development ARP Report, p. 24]

NIH should continue to encourage the use of small animal models (such as cats and mice) for the development and assessment of vaccine concepts.

These animals provide the opportunity to examine large numbers of variables and group sizes in a relatively short time frame and at relatively modest cost. However, the value of large-animal studies not involving primates or an SIV or HIV challenge should be judged critically for their potential contribution against the substantial cost of these models.

Current Status

Where appropriate, NIH encourages the use of small animals (mice and guinea pigs) in R01 and U01 (cooperative agreement) grants for the initial testing of vaccine concepts for induction of immunity. Standardized rabbit studies for safety of novel adjuvants have been developed jointly with NIAID and the FDA. Where viral or bacterial vaccine vectors do not permit growth and assessment because of species restrictions in small animals, a case can be made for proof-of-concept testing in nonhuman primates. Such studies are handled on a case-by-case basis in the review of grant applications and in requests for grant supplements involving vaccine designs that have successfully advanced to this level of testing. Analysis of multiple subgroups of nonhuman primates for multiple parameters is usually not possible and has been reserved for comparative studies. Vaccine animal model studies in cats with feline immunodeficiency virus (FIV) or in horses with equine infectious anemia virus (EIAV) have been funded where a specific advantage to the studies can be demonstrated.

Future Actions

NIH will continue to encourage investigators to develop appropriate small animal tests for initial investigation of vaccine designs that require assessment of multiple parameters. Information will be distributed to initial review groups to indicate that this type of experimentation often is highly appropriate in early stages of vaccine design and development.

Recommendation 234 [Vaccine Research and Development ARP Report, p. 25]

NCI and NIAID should reevaluate their code assignment procedures to ensure that a more accurate representation of what basic and preclinical research is devoted to the NIH vaccine program.

The Panel believes that the approximately $113 million sum defined as the cost of the vaccine research and development by NIH for FY 1994 significantly overestimated the true expenditure on these programs. Miscoding also might have underestimated the expenditure on basic research in some areas of immunology.

Current Status

NIAID

NIAID agrees with the Panel that the coding of vaccine projects for FY 1994 (the data evaluated by the Area Review Panel) was confusing. Unavoidable artifacts are inherent in any coding scheme devised for complex, interactive scientific research (such as AIDS vaccine research). Since the FY 1994 coding, there has been greater clarification between OAR and ICDs about what should and should not be included in "vaccine research" as defined by the NIH Plan for HIV-Related Research. For FY 1995 and FY 1996, only those funds that were spent on vaccine research or preparedness for efficacy trials were coded by NIAID as "vaccines." Biomedical prevention research is now reported under the natural history, epidemiology, and prevention section of the plan.

In addition, because of the overlapping nature of the coding scheme, there remains some difficulty in accurately reporting research on basic immunology. NIAID has developed specific guidelines for identifying "AIDS-related" research; these guidelines were presented to OAR and received its concurrence. Accordingly, immunology research may appear coded as "vaccines," "natural history, epidemiology, and prevention research," or as "etiology and pathogenesis." In addition, NIAID funds a substantial portfolio of research on human immunology that is not reported to the OAR as AIDS or AIDS-related since it is funded with non-AIDS dollars but provides a broad scientific context for NIAID's AIDS research.

NCI

NCI recognizes the problems and inconsistencies that may have occurred prior to FY 1996 with respect to its assignment of OAR Strategic Plan codes to intramural research projects in the areas of AIDS pathogenesis, vaccine, and therapeutics research. The problem was first highlighted in the May 1995 report "A Review of the Intramural Program of the National Cancer Institute: Recommendation of the National Cancer Advisory Board *Ad Hoc* Working Group" (Bishop/ Calabresi Report). This problem in reporting may have led to an overestimate of NCI resources committed to AIDS vaccine research and an underestimate of resources committed to research on

viral pathogenesis and human immunology. In October 1995, the NCI Executive Committee reviewed the Institute's AIDS research program and determined that significant reallocation of resources would take place in FY 1996 within all areas of both the Institute's intramural and extramural AIDS research programs, along with a reevaluation of OAR Strategic Plan codes for each project. In FY 1994, NCI allocated $14.4 million for AIDS vaccine research, representing only 6.8 percent of NCI's FY 1994 AIDS research budget. The FY 1995 expenditures for AIDS vaccines dropped to $8.4 million (3.9 percent of NCI's AIDS budget), with all of the reduction occurring in the contract line. NCI estimates that for FY 1996 it has spent approximately $8.3 million (3.7 percent of its AIDS budget) on AIDS vaccines.

Future Actions

NIAID and NCI will continue to code their research according to their understanding of the NIH Plan for HIV-Related Research. NIAID and NCI also will continue to review and revise their "AIDS-related" guidelines to ensure that they reflect new developments and current research priorities.

Recommendation 235 [Vaccine Research and Development ARP Report, p. 25]

NIH should place a very high priority on the creation of a new study section dedicated to fundamental vaccine research topics, either de novo *or from existing AIDS-related study sections.*

OAR should work with DRG to ensure that this is done as rapidly and as efficiently as possible. The academic standards of successfully competing awards should be maintained in vaccine research at a common, high level, as in all areas of AIDS research. Because some vaccine research may not be considered cutting edge science by the existing study sections, the new study section should include individuals who recognize the imperative need for translational research in vaccines. Such individuals should be sought to ensure adequate unsolicited R01 funding.

Please refer to the NIH response to Recommendation 8.

Recommendation 236 [Vaccine Research and Development ARP Report, p. 25]

Both NIAID and NCI should minimize the amount of funds allocated by Program Staff without outside peer review from contractual or other resources available within these Institutes.

A detailed breakdown of such supplementary funds should be provided to OAR on an annual basis. Distribution of funds through the Master Contract (in NIAID) and other contracts in NCI should be determined by a review group comprised of both intramural and extramural scientists, in addition to NIH Program Staff and administrators.

Current Status

NIAID

NIAID recognizes the need for full peer review and, therefore, the need to minimize the amount of funds allocated without peer review. However, in the context of an epidemic and fast-moving science, the need for flexibility also is critical. A balance must therefore be struck in order to expedite research in newly developing scientific areas and to take advantage of unique opportunities linked to technological developments. For example, supplemental funds were made available in the past few years to "jump-start" research on chemokines and acute HIV infection and to provide funds for viral load determinations using more sensitive RNA polymerase chain reaction (PCR) techniques. NIH has well-documented policies whereby administrative supplements may be made for specific purposes.

Distribution of funds through the Master Agreement Contracts is peer reviewed, and oversight is provided by NIAID review staff. In addition, the VDEG reviews projects using animal resources to be funded through this mechanism. The AVRC, when it is constituted, also may provide oversight for the Master Agreement Contract.

NCI

As discussed in the more detailed NIH response to **Recommendation 234**, NCI has reduced its expenditures on many AIDS contracts and modified contracting procedures to minimize the resources that can be allocated in the absence of additional peer review.

All ICDs

Supplements provided to grants or contracts funded by the ICDs through the OAR Discretionary Fund are independently reviewed by OARAC. All supplements made by the ICDs are reported to OAR at the end of the fiscal year along with all other information on grants and contracts.

Recommendation 237 [Vaccine Research and Development ARP Report, p. 25]

> *A relatively small sum of seed money (perhaps derived from the OAR Director's Discretionary Funds) could be placed under the control of an expert peer-review group, specifically to allow vaccine concepts to be evaluated in primates before submission of a more formal research proposal.*
>
> *The Panel fully appreciated that the R01 mechanism was not necessarily the most suitable way to fund some key areas of AIDS vaccine research and development. Vaccine research can have an empirical nature that is not well-recognized by study sections, and can be unusually expensive compared with certain other areas of AIDS research. A less abstract problem is that study sections require, not unreasonably, evidence of preliminary data that support the feasibility of a concept under review. Without such data, an application may well be denied funding, irrespective of its intrinsic merit. Yet*

without such funds, it may be impossible to obtain appropriately convincing data, especially if experiments involving primates are necessary. This vicious cycle needs resolution.

Current Status

NIAID agrees that it is often difficult for investigators to obtain funding for empiric research or development through the standard peer-review process, and NIAID has discussed this issue with ARAC. The Institute has several programs in place that stimulate this type of research and allow some degree of flexibility for investigators seeking to do empiric vaccine research. The NCVDG program specifically includes funds for preliminary studies in primates. In addition, the Simian Vaccine Evaluation Units (SVEUs) are available to perform initial studies on novel and promising vaccine concepts in collaborative research. NIAID also provides additional funding opportunities for *in vivo* research through its PAs and opportunities for competitive supplements for research related to pathogenesis and vaccine research (such as the PA on "Mechanisms of AIDS Pathogenesis"). In addition, NIAID relies on expert guidance from its vaccine groups, such as the VDEG and the AVRC, to recommend studies for support within the Vaccine Preclinical Master Agreement Contract.

Future Actions

NIAID will continue to work with its investigators to see that early primate evaluation of vaccine concepts can be accomplished. It is anticipated that the AVRC will be helpful to NIAID on this issue and will work with OAR and DRG on the issue of a study section for vaccine research. As suggested, NIAID will, when appropriate, request OAR supplemental funds to assist in supporting such empiric research.

Recommendation 238 [Vaccine Research and Development ARP Report, p. 26]

Basic research activities should not be supported under the existing contract mechanisms.

Contracts are time-consuming and expensive to compete for and to administer, both in terms of financial costs and of demands on scientists' time. The necessarily rigid legal constraints imposed by the nature of a contract are not always compatible with the flexibility that is an integral component of cutting-edge research. NIAID basic vaccine research funds currently allocated to contracts should be shifted to grant mechanisms. Targeted R01 awards or cooperative agreements (U01) were perceived to be superior mechanisms for enabling key areas to be studied, while allowing investigators the independence to achieve scientific goals in the way they consider most appropriate.

Current Status and Future Actions

NIAID agrees that, in general, basic research should not be supported by contract mechanisms. The Institute has, over the past several years, systematically moved major programs from contract to grant mechanisms. A recent systematic staff review of the entire NIAID contract portfolio identified only one contract under which basic research is still being conducted. That contract, on the advice of NIAID's Advisory Council, is being converted to a cooperative agreement. NIAID's remaining contracts are used only for procurement of specific information, services, and/or products that directly support and benefit the Government.

Recommendation 239 [Vaccine Research and Development ARP Report, p. 26]

> *The Panel urges review committees and Program Staff to recognize the clear requirement for more support for investigator-initiated research and encourages review committees to approve the necessary support in appropriate circumstances.*
>
> *In many cases, small-to-medium sized R01 grants are suitable, and the scientific return on such investments can be considerable. However, funding limits often preclude the support of such studies through the conventional R01 mechanism. Three mechanisms by which adequate resources might be obtained are: increasing the funding ceiling on R01 awards under certain circumstances; reinstituting Program Project (P01) awards similar to those provided by other ICDs; and increasing funds for the NCVDG or unsolicited cooperative agreements (U01s).*

Current Status

NIAID agrees fully with the Panel that it has been difficult for investigators with vaccine concepts to obtain funding, through the standard peer-review process, for many of the more expensive aspects of vaccine research, such as studies in animals and humans. To address this problem, NIAID has made an effort in recent initiatives to stress investigator-initiated research and to provide researchers with more flexibility in choosing funding mechanisms appropriate for the scope of their research. For example, most PAs now list several mechanisms from small grants (R03s), which allow the gathering of preliminary data, to large R01s, U01s, and P01s, which allow consortial arrangements within one grant. In addition, NIAID allows for special actions, which are taken with its Council's concurrence, to restore budgets above the limits recommended by the IRGs. This mechanism has been used successfully to fund large grants including those to support animal research.

The NIAID Advisory Council has expressed concern to the NIH Director about the steep rises in animal care and research costs and the continued need to support animal resources. Thus, any recommendations for AIDS research should be considered in the broader context of animal research supported across the NIH.

Future Actions

NIAID plans to continue funding the highly meritorious investigator-initiated research related to vaccine design and development through a variety of mechanisms. New initiatives are being developed with the intent of providing investigators with maximum flexibility for funding opportunities. For FY 1998, NIAID will release a PA that will expand the NCVDG program and institute a SPIRAT-like program designed to bridge preclinical and early clinical development and testing of novel vaccine concepts. These programs are being initiated to build on the current efforts to increase basic discovery and design of novel vaccine approaches.

Recommendation 240 [Vaccine Research and Development ARP Report, p. 26]

The U01 and U19 mechanism used to support the NCVDGs for conducting multidisciplinary studies of potential AIDS vaccines merits increased support, whereas the interactive R01 mechanism for multidisciplinary studies should be abolished.

The U01 and U19 cooperative agreements retain administrative flexibility and encourage cross-talk between basic research investigators and preclinical study investigators. However, the Subpanel was particularly concerned that the current cap on funds for these awards precludes or substantially limits basic concept testing in primate models.

Current Status

NIAID currently supports a number of programs utilizing the cooperative agreement (U01 and U19) mechanism. Consistent with NIH policy, interactive R01s remain an option for unsolicited applications.

Recommendation 241 [Vaccine Research and Development ARP Report, p. 26]

To enhance the functioning of both the vaccine development oversight group proposed above (discussed further in the Targeted Vaccine Research Subpanel report) and the efforts of extramural investigators, NIAID should establish and monitor a comprehensive computer database for recording and analyzing information derived from vaccine trials in animals and humans.

This information should be routinely available to all grantees involved in AIDS vaccine research to permit coordinated efforts to critically evaluate different experimental approaches and develop valid cross-comparisons of data.

Current Status

NIAID recognizes and appreciates the value of standardization and comparisons across different vaccine approaches and studies. To further those efforts, NIAID already has instituted centralized laboratories for both human and nonhuman primate clinical studies. Data from these laboratories

are published, along with the study results, in peer-reviewed literature. In addition, NIAID makes available information about what studies are ongoing in both the AVEG and the SVEUs. However, there are complex scientific, ethical, and legal issues involved in making data from ongoing trials or preclinical research databases available to the general scientific community. Such databases are working databases and often contain preliminary data or confidential patient and/or proprietary information. Legal issues of data ownership also are a major factor.

Future Actions

NIAID is examining ways to provide a centralized source of information about vaccine trials that are completed or ongoing. As it has done with treatment trials and epidemiology studies, NIAID will investigate the possibility of making available to the public, through the National Technical Information Service, those data sets from vaccine trials that have been completed and published, after confidential and proprietary information has been removed.

Recommendation 242 [Vaccine Research and Development ARP Report, p. 27]

> *The need for an RFA should be reviewed by an expert group comprised of both extramural non-Government scientists and DAIDS Program Staff.*
>
> *The charge to that group would include a careful review of study section-approved proposals to address whether work supported by the proposed solicitation would overlap with other supported or planned programs. NIAID should retain its current policy of funding only those proposals considered sufficiently meritorious and not pre-allocating a fixed sum to an RFA.*

Current Status and Future Actions

NIAID believes that its current practice of concept clearance for all initiatives is consistent with the goals of this recommendation. Over the last several years, NIAID has decreased its use of targeted RFAs. For example, RFAs are now used almost exclusively for multicenter clinical trials or natural history studies that require centralized coordination, or when a priority research gap has not been filled by investigator-initiated research stimulated by PAs. Basic research is supported through the use of PAs that include a variety of mechanisms, such as R01, R29, R03 (small grants), interactive R01s, and P01s. This shift is designed to increase the flexibility that investigators have in selecting funding mechanisms best suited to their research scope.

NIAID develops initiatives in concert with focus groups, workshops, or informal discussions with investigators who assist the Institute in defining the scientific areas of need. All initiatives are subsequently reviewed and approved in concept by NIAID's Advisory Council and the ARAC. This concept clearance is an NIH-mandated part of any initiative development. As part of this exercise, ARAC considers whether the mechanism of solicitation (RFP, RFA, PA, etc.) is appropriate for the scientific need; ARAC also reviews the initiative for potential overlap with other new or ongoing activities. The funds associated with a particular concept are always conditional upon receiving proposals of sufficient scientific merit.

Recommendation 243 [Vaccine Research and Development ARP Report, p. 27]

NCI should immediately conduct a rigorous review of all components of its intramural program presently designated as contributing to AIDS vaccine research and development and use this review to determine which of its current vaccine-related programs should be preserved, and at what level of support.

The Panel was concerned that many projects coded in this area bore little or no relevance to the reality of vaccine research and development. Thus their inclusion within the vaccine budget substantially distorts the perception of the actual NIH effort expended on vaccine development. Indeed, a substantial proportion of dollars assigned to NCI intramural vaccine research probably should not be considered as AIDS-related in any sense.

Current Status and Future Actions

In 1994, the National Cancer Advisory Board convened a panel of outstanding cancer researchers to conduct a complete review of NCI's intramural research programs in cancer and AIDS. A number of perceived problems were highlighted in its May 1995 Bishop/Calabresi Report. On August 1, 1995, Dr. Richard Klausner was appointed Director of NCI and set into motion a complete reorganization of the Institute based in large part on many of these recommendations.

NCI has completed much of this reorganization, including locating intramural and extramural research programs into different operating divisions. The intramural research program now consists of three divisions: the Division of Basic Science, Division of Clinical Science, and Division of Cancer Epidemiology and Genetics. The extramural programs are located in the Division of Cancer Biology; the Division of Cancer Treatment, Diagnosis, and Centers; the Division of Cancer Prevention and Control; and the Division of Cancer Epidemiology and Genetics. A rigorous nongovernmental peer review of each intramural program, laboratory, and component project was initiated. The first cycle of site visits for all intramural laboratories will require 3 years, during which time any cancer or AIDS projects determined to be weak or of less importance will be phased out, and those considered high priority to NCI's scientific missions in cancer or AIDS may see an increase in their resources. In less than a year, entire programs have been abolished and other scientific programs have been realigned.

Recommendation 244 [Vaccine Research and Development ARP Report, p. 27]

The Subpanel proposed that AIDS vaccine research activities of the NIH might best be served if the most relevant and competitive intramural programs at the NCI were placed within a single Division, with administrative control by the OAR, with the view of assimilation into the NIAID intramural program.

In nearly all cases, it should be possible to achieve this goal without the necessity for physical relocation of any research groups. The facilities at the FCRDC could be used

for a targeted, coordinated national effort towards developing an AIDS vaccine. At the very least, the coordination of AIDS programs at NCI needs to be under the administrative review of the OAR until the creation of a unified, cohesive AIDS vaccine program within the NIH.

Current Status and Future Actions

A major effort to concentrate NCI efforts to develop an AIDS vaccine at the Frederick Cancer Research and Development Center (FCRDC) is under consideration, and recruitment of a distinguished scientist to direct this effort is in progress. Although all of NCI's vaccine research will be coordinated with that of other ICDs and OAR, it should remain under the administrative and scientific direction and authority of NCI.

Recommendation 245 [Vaccine Research and Development ARP Report, p. 32, No. 1]

NIH should institute a mechanism for accomplishing targeted vaccine research.

Current Status

NIAID has four mechanisms in place to facilitate targeted preclinical vaccine research:

- NCVDGs, (U01), which funds investigator-initiated research that is solicited in cycles that permit regular renewal.

- SIV Vaccine Evaluation Units, which are funded through contracts that perform animal vaccination studies under specified conditions. These were funded for 5 years beginning in FY 1996. Animal resources on these contracts can be made available to investigators with funded NIH grants and with the approval of the NIAID VDEG to investigators with novel vaccine ideas who do not have access to other primate resources.

- Preclinical Master Agreement Contracts for preclinical studies, which can be made through Master Agreement Contracts that are competed on an annual basis. Awards through these contracts can be funded in a minimum of 4 to 6 months.

- Immunological studies on macaques, which can be performed on an "as needed" basis through other contracts with laboratories that conduct either standardized serological studies or cellular immunity studies planned and coordinated with the investigators in charge of the study.

The AVEG also does targeted vaccine research in human subjects. The AVEG evaluates new HIV vaccine candidates as they become available in Phase I and II trials, performing standard immunological assays so that different candidates or vaccine approaches can be compared.

Future Actions

In addition to renewal of the NCVDGs, a new form of NCVDG awards will compete for funding in FY 1998. These investigator-initiated cooperative agreements will be able to provide basic and developmental resources for vaccines beyond preclinical testing and through preparation of clinical materials and initial testing in human subjects.

Options will be discussed to determine whether additional funding through existing mechanisms can be used for trans-NIH funding of targeted vaccine research.

Recommendation 246 [Vaccine Research and Development ARP Report, p. 33, No. 2]

NIH should establish a team of extramural-intramural experts for centralized direction of HIV/AIDS targeted vaccine research.

Current Status

NIAID has developed a team of intramural and extramural program staff scientists to provide review, coordination, and centralized direction of targeted vaccine research. This VDEG was formed in 1995 and functions to advise NIAID about use of the resources committed to targeted vaccine research, primarily in nonhuman primates. This team currently does not review the needs for AIDS vaccine contracts supporting intramural research in either NIAID or NCI and is not linked to the AIDS Coordinating Committee formed by NCRR for the RPRCs.

Future Actions

In addition to the extensive input and advice provided by the NIAID VDEG mentioned above, coordination and integration of targeted research funded by other ICDs was recommended. The AVRC will not only provide continual guidance and review of the preclinical progress on candidate HIV vaccines but also serve in an advisory capacity to the Director, NIAID, regarding decisions based on research to accelerate products to clinical trials. Further decisions about coordination of cross-Institute preclinical vaccine research will be made by the AVRC.

In addition, please refer to the NIH responses to Recommendations 15 and 231.

Recommendation 247 [Vaccine Research and Development ARP Report, p. 34, No. 3]

The NIH should provide additional funds for targeted vaccine development.

Current Status

NIH is providing additional funds for targeted vaccine development.

OAR has provided resources requested by NIAID in the FY 1997 budget for vaccine-related research. In addition to the funds previously requested by NIAID, $6 million has been added to the Institute's commitment base in FY 1997 to allow the Institute to respond effectively to opportunities identified by the AVRC. It is anticipated that a substantial proportion of these resources will be used for basic and targeted preclinical research. Approximately $2.5 million in additional funds was allocated to NCRR for collaborative investigator-initiated projects in nonhuman primate research on pathogenesis and AIDS vaccines. An additional $1 million currently is reserved in the OAR budget for vaccine research. Further one-time allocations may

be made for peer-reviewed vaccine research from the OAR Discretionary Fund if the need is demonstrated by ICD program scientists and the OARAC approves such ICD requests.

Future Actions

To take advantage of expanding opportunities in FY 1997, vaccine researchers are being encouraged to submit grant applications or competitive supplements to existing grants for HIV/AIDS vaccine research for the DRG deadlines for AIDS-related research applications. In addition, NIAID has issued a PA to solicit grants or supplements to existing grants to explore novel vaccine concepts. Additional solicitation of investigator-initiated research in AIDS vaccines and mucosal immunity through RFAs and PAs is anticipated for FY 1997 and FY 1998.

OAR will continue to prioritize vaccine research at the highest level.

Recommendation 248 [Vaccine Research and Development ARP Report, p. 34, No. 4]

Importance of establishing new funds for a new area of NIH activity.

Current Status

OAR agrees that new funds should be made available for new or expanded efforts in targeted HIV/AIDS vaccine research without adversely affecting the other ongoing efforts in AIDS vaccine research. These funds would support a balanced program of nondirected, investigator-initiated research, targeted developmental preclinical and clinical testing, and efficacy testing when appropriate milestones are met. In addition to the $6 million specified above (see response to **Recommendation 247**) for new initiatives in vaccine research, OAR has approved RPG funds for basic research in the immunology and pathogenesis of HIV for FY 1997.

Future Actions

The NIH AIDS allocation for the ICDs for FY 1998 will be formulated by OAR in the spring of 1997. At the same time, the AVRC will work with the OAR HIV/AIDS Vaccine Coordinating Committee to develop the vaccine component of the FY 1999 NIH Plan for HIV-Related Research to enable NIH to identify gaps and new areas that need attention.

CLINICAL TRIALS RESEARCH SUBPANEL

Recommendation 249 [Vaccine Research and Development ARP Report, p. 48]

> *The poor economic prospects for vaccine development appear to be a restraining force on the entire vaccine development effort.*
>
> *OAR, as a high priority, should invest resources in analyzing and proposing solutions to this problem. It may need to attract more industrial-sector participation or consider cooperative or public ownership arrangements for AIDS vaccine products, especially for riskier approaches.*

Current Status

The lack of a strong private-sector interest in the development of HIV/AIDS vaccines clearly stems from multiple and complex concerns—some of which are scientific in nature—that have repeatedly presented difficult challenges to vaccine design. A review of private enterprise needs for vaccine research conducted by the nongovernmental AIDS Vaccine Advocacy Group, released December 1, 1996, identifies a number of issues.

OAR supports the reinvigoration of the HIV/AIDS vaccine effort through expanded funding of basic and developmental research, including clinical trials research to resolve some of the scientific concerns impeding private-sector involvement in HIV vaccine research. NIAID has specifically developed a vaccine strategy to encourage early contact with companies and more cooperation with developmental testing. A number of revisions of the SBIR program now permit faster movement from SBIR Phase I grants to Phase II grants and the further encouragement of joint efforts between academic institutions and small businesses. NIH will make additional efforts to encourage vaccine research and product development through the SBIR program.

Future Actions

The AVRC and OAR will carefully consider the perspective provided by the AIDS Vaccine Advocacy Group and other organizations. In the interim, efforts will be made to publicize new initiatives in targeted vaccine research that might trigger private-sector interests and provide new insights to the design and delivery of vaccines.

Recommendation 250 [Vaccine Research and Development ARP Report, p. 49]

> *It is essential that AVEG and DAIDS Program Staff establish a mechanism to allow scientists to request collaboration with contracted programs for studies with clinical samples, with some funds set aside to support such collaborations.*

Current Status

Strengthening the linkage between the scientists working with the cohorts and "outside" investigators remains of the highest priority to NIAID. NIAID has prepared and is now distributing (in hard copy and via the NIAID Web site) a document to help scientists form collaborations with the epidemiologic cohort and clinical trial groups that NIAID supports. The document describes, in general terms, the material and data sets of each study, as well as processes and lists of contacts for each group. NIAID does not favor set-aside funds to be used for collaborations with specific groups, such as the AVEG, but instead encourages peer-reviewed collaborative research that builds on NIAID clinical trials and natural history studies.

Future Actions

NIAID and the AVEG will continue to work to inform investigators of the possibilities for collaborations with the clinical trials group.

Recommendation 251 [Vaccine Research and Development ARP Report, p. 49]

> *Criteria for advancement of candidate HIV vaccines should be determined in advance. The decision-making process must be open (i.e., including participation of both the larger scientific and affected community), more clearly defined, and with a specific person or group that has final decision-making authority.*

Current Status

NIAID has developed a model process outlined in the paper "NIAID HIV/AIDS Vaccine Research and Development: Strategy and Opportunity," which has been distributed at several meetings. The general principles for establishing guidelines for vaccine products/concept focused on initiation of Phase III trials are prospectively addressed. Specific guidelines for each vaccine concept are then outlined in the Development Plans section. These plans are constructed in concert with the vaccine sponsor, the vaccine advisory groups, the extramural investigators, and community representatives involved in the testing of these vaccines at AVEG and HIVNET sites. These plans include specific milestones/goals that must be achieved by the vaccine candidate and provide opportunities for decision points and reevaluations based on new scientific information.

Future Actions

As indicated in the NIH response to **Recommendation 15**, NIH anticipates that the AVRC will, in addition to providing continuous guidance on the process for advancing candidate HIV vaccines, serve in an advisory capacity to the Director, NIAID, regarding decisions to proceed to efficacy trials.

Recommendation 252 [Vaccine Research and Development ARP Report, p. 49]

Therefore, new Phase I and Phase II trials should continue to be a high priority even if one or more vaccines advance into efficacy trials.

Current Status

Most of the HIV vaccine clinical trials currently supported by NIH through NIAID are Phase I trials of safety and immunogenicity and are evaluated by the NIAID-sponsored AVEG. As new vaccine candidates or concepts become available, NIH will continue to place a high priority on testing them—either alone or in combination with other candidates or concepts—and new delivery systems in human volunteers.

Future Actions

With the limited knowledge that exists concerning HIV vaccines in human subjects, NIH is committed to continue testing new candidate vaccines in human volunteers to determine immunogenicity in the relevant host. Products in Phase I and Phase II trials will be advanced if they meet appropriate milestones.

Funding for the AVEG contracts recently has been renewed and should be appropriate for the next few years. Funding needs will be reviewed in a timely manner by NIAID and OAR to ensure adequate budget planning. Only one Phase II clinical trial has been conducted in the past, and one is currently planned to be initiated in FY 1997.

In addition, please refer to the NIH response to Recommendation 251.

Recommendation 253 [Vaccine Research and Development ARP Report, p. 49]

OAR should develop a process to assist with and review the allocation of resources and coding of projects in the AIDS budget.

Please refer to the NIH response to Recommendation 44.

Recommendation 254 [Vaccine Research and Development ARP Report, p. 49]

NIH should retain the commitment to international trials and scientific collaborations, given the global nature of this disease.

Current Status

NIH-sponsored basic research in international vaccine development includes continued studies to assess HIV-1 genetic variants isolated from international sites, serological studies to understand the mechanisms of cross-clade neutralization, and efforts to develop vaccine concepts that might

be appropriate both in terms of their ability to generate specific immune responses and to be delivered at reasonable cost. These studies are primarily funded through NIAID, with additional studies supported by NCI, FIC, or NCRR. NIH also sponsors research assessing the seroconversion rate needed for vaccine protocol development in a number of countries through the NIAID-sponsored HIVNET and investigator-initiated projects. Other collaborative efforts sponsored by FIC and NIAID are seeking to build research capacity at international sites by providing training to foreign scientists so that they are better able to conduct clinical trials of vaccine candidates and to evaluate immunological parameters in vaccine trials.

Future Actions

NIH fully intends to retain its commitment to research on the design, development, and evaluation of vaccines that might have broad applicability and the potential to blunt the wide HIV/AIDS pandemic. These activities span efforts from basic and developmental research in novel vaccines to the conduct of clinical trials in appropriate international sites.

Basic research and vaccine development as well as capacity building are ongoing. NIH, through NIAID and FIC, plans to continue its strong commitment in these areas. The first NIH-sponsored Phase I trial at an international site is being planned in conjunction with the Ugandan Government and with the assistance of UNAIDS for initiation in FY 1997. This trial is essential to address a critical research question about the induction of cross-clade CTL by a clade B vaccine candidate, which contains multiple HIV genes, when administered to individuals whose ethnic and racial backgrounds differ from those of individuals already being studied in the United States and Europe. Other trials will be planned when they are determined to be technically feasible; when the cohorts of volunteers appear to be appropriate to address scientific questions of immunogenicity, safety, and/or efficacy; and when personnel at the sites are adequately trained to conduct clinical trials.

Recommendation 255 [Vaccine Research and Development ARP Report, p. 50]

> *Significant resources should be directed toward using clinical trial networks (AVEG and HIVNET cohorts) to advance our overall knowledge of the immune responses to vaccine strategies.*

Current Status

NIAID and the AVEG and HIVNET investigators agree that research aimed toward understanding immune responses to vaccines is a critically important focus of clinical research. The AVEG protocols include intensive evaluations of immune responses to HIV vaccines. To facilitate these studies, the AVEG includes two centralized immunology laboratories, one of which focuses on mucosal immune responses. Much of the research being conducted in conjunction with the AVEG protocols is applicable more broadly to other human immune responses. In addition, these laboratories are developing and standardizing new assays and sample collection protocols that will benefit research on other vaccines. The joint AVEG and HIVNET protocols that are currently being developed will continue an emphasis on the

immunological characterization of responses to HIV vaccines. In addition, the AVEG has an intensive protocol for followup of vaccinees who become infected.

HIVNET also conducts extensive immunological studies as part of the vaccine readiness and prevention protocols that it conducts. An important part of this research is to establish appropriate "standard" immunological profiles for the populations that are at highest risk for HIV infection.

Future Actions

NIAID will continue to facilitate and support intensive study of the immune responses of vaccinees to HIV antigens. More detailed studies will continue to be preformed on a subset of volunteers. To accomplish this, NIAID has submitted a request to OAR to expand the capacity of the centralized immunology laboratories associated with the AVEG and HIVNET.

Recommendation 256 [Vaccine Research and Development ARP Report, p. 50]

> *Laboratories linked to the clinical trials effort should focus on automation of routine assays, development and validation of new and better assays, and more comprehensive studies of the human immune responses to vaccination. It is particularly important that methods to quantify cellular responses, especially CTL, be encouraged.*

Current Status

Both the AVEG and the HIVNET have centralized laboratories incorporated in their organization that perform the majority of immunological tests on vaccinees and participants in trials. The rationale for these centralized resources was to increase efficiency through automation and larger scale performance of routine assays. In addition, these laboratories develop and scale-up new assays, as well as provide validation and quality control for new and routine assays.

As noted in the NIH response to **Recommendation 255**, the AVEG and HIVNET perform extensive evaluations of immune responses to HIV vaccine antigens. One area of particular interest in the past few years has been the generation of cellular responses to HIV antigens. Studies of CTL generation and targeting of immune cells (such as CTLs) to mucosal sites have been peer reviewed and are under way by AVEG and non-AVEG investigators. Additional studies are examining the fine specificity of HIV-specific CTLs. OAR has provided supplemental funds over the last several years to expand these studies.

Recommendation 257 [Vaccine Research and Development ARP Report, p. 50]

> *NIAID should streamline mechanisms for ensuring access to specimens for investigators outside of AVEG/HIVNET and ensuring available funding for specialized studies.*

Current Status

Strengthening the linkage between scientists associated with the cohorts and independent investigators is critical to NIAID. NIAID has prepared and is distributing a document to help scientists form collaborations with the clinical trial and natural history groups that NIAID supports—such as the AVEG and HIVNET. NIAID favors peer-reviewed and investigator-initiated research grant mechanisms as the optimal source of funding for such research.

Future Actions

NIAID and AVEG and HIVNET will continue to work to make investigators aware of the possibilities for collaborations with the clinical trials groups.

In addition, please refer to the NIH response to Recommendation 250.

Recommendation 258 [Vaccine Research and Development ARP Report, p. 50]

NIAID should be more active in seeking out and assisting in the production of pilot lots of vaccine candidates, if needed, to test new vaccine strategies.

Current Status

NIAID agrees that support for production of pilot lots of vaccines candidates may sometimes be needed. In most instances, this would be accomplished best by funding production by the vaccine developer/sponsor (company or investigator). NIAID has submitted a request in its FY 1998 budget submission that would allow for funding to produce specific pilot lots of vaccines or to assist with other specific steps in vaccine development.

Future Actions

NIAID will work with the new AVRC to identify situations in which the critical need for one or more pilot lots is the limiting factor in the evaluation of a novel or worthy vaccine concept.

Recommendation 259 [Vaccine Research and Development ARP Report, p. 50]

NIAID should dedicate additional personnel or resources to facilitate the trials "start up" process (protocol development, satisfying FDA requirements, filing investigational new drug [IND] applications, making arrangements with manufacturers) to enter candidate vaccines into Phase I/II trials and ensure effective use of the AVEG trials network.

Current Status

NIAID scientific and regulatory staff, as well as NIAID-supported investigators, agree that obstacles to rapid clinical evaluations should be minimized, and NIAID and its investigators will continue to strive to improve the efficiency of programs. However, there is almost universal agreement that the most serious problem in initiating trials at this time is the availability of vaccine candidates prepared for human studies. The potential for NIAID support for production of pilot lots of vaccine is addressed in the NIH response to **Recommendation 258**.

Future Actions

NIAID will continue to seek ways to improve the efficiency of its vaccine clinical trials groups and to engage the private sector in addressing issues related to vaccine trials. In addition, the expanded NCVDG initiative proposed for FY 1998 will provide a more flexible process for evaluating very early vaccine concepts.

Recommendation 260 [Vaccine Research and Development ARP Report, p. 50]

> *NIAID should establish a rigorous plan and schedule for deciding the future direction of HIVNET as soon as possible. HIVNET, or selected components, should be decreased in scope or eliminated after baseline studies are completed, unless clearly appropriate vaccine or nonvaccine intervention trials are undertaken or anticipated in the near future.*

Current Status

A detailed plan was developed in 1996 by HIVNET investigators and NIH staff. In June 1996, NIAID and OAR convened a multidisciplinary panel of experts to conduct a review of HIVNET organization, governance, research, and funding. This review included participation from other ICDs with research expertise relevant to HIVNET's activities. This review was conducted under the auspices of NIAID ARAC. A report of the review and the recommendations was presented to the ARAC and accepted by that group in September 1996. A summary of the review and recommendations also was presented to the OARAC in October 1996.

In its report, the panel expressed confidence in HIVNET. They found the scientific plan and program of research to be sound. In addition, the panel noted that there had been considerable progress and maturation of HIVNET since the time of the NIH AIDS Research Program Evaluation Task Force review. The panel provided a number of constructive recommendations to further improve HIVNET, including the following:

- HIVNET should be continued and should give priority to its original mission, which is to provide the capacity for prompt and scientifically sound assessment of vaccine efficacy both domestically and internationally.

- HIVNET must continue to maintain a strong multidisciplinary approach to maintain or develop its capacity for evaluating both vaccine and nonvaccine interventions.

- In addition to the ongoing program of research related directly to vaccine efficacy trials, HIVNET's domestic and international cohorts provide a valuable resource for evaluating other biomedical and behavioral interventions for preventing sexual, parenteral, and perinatal transmission of HIV. Inter-Institute/agency collaboration for microbicidal and perinatal transmission studies and OAR-based coordination for behavioral studies are essential for defining the scope and setting priorities for these non-vaccine-based activities.

- For non-vaccine-based activities, prioritization and implementation plans should include clearly articulated guidelines for the choice of product or interventions. For microbicides and perinatal transmission research, these guidelines should include the potential global availability of products, biological endpoints, and individual rather than community intervention strategies. Behavioral research should focus on descriptive or methodological studies essential for the conduct of vaccine trials. When promising behavioral interventions have been identified as suitable for testing in HIVNET, they should be tested using HIV infection as the trial outcome measure.

Future Actions

NIAID program staff will continue to work with HIVNET investigators to implement the research priorities outlined in the scientific agenda proposed by the investigators and endorsed by the review panel. Recommendations of the panel are being incorporated into the operation of HIVNET.

In addition, please refer to the NIH response to Recommendation 264.

Recommendation 261 [Vaccine Research and Development ARP Report, p. 50]

More of HIVNET's resources should be devoted to educating communities that will eventually participate in trials.

Current Status

NIAID recognizes the importance of community education and remains committed to working with the communities most at risk and affected by the AIDS epidemic to ensure continued progress toward effective preventive measures and treatments for HIV infection and AIDS. NIAID program staff, HIVNET investigators, and community representatives are currently developing a community education plan. One of the major avenues for community education is through the national and local CABs. In addition, NIAID solicits community input to its research efforts through participation of CAB members in governing bodies of research groups, inclusion of community members on all program review panels, and community representation on its advisory committees such as the NIAID Advisory Council and the ARAC. In addition, NIAID has encouraged community participation in scientific meetings it sponsors by providing travel funds. NIAID views these educational activities for community representatives as an integral part of education to the broader community.

In addition, NIAID has encouraged all of its clinical trials and natural history groups, including HIVNET, to develop specific plans for community outreach and education. For example, some sites provide English and Spanish newsletters and videotapes about the research efforts. Scientists and local recruiters from the sites actively seek out ways to meet with the community and provide education about HIV infection and their research. NIAID also funds, mainly through its SBIR program, development of educational materials about HIV infection, prevention, and treatment. Program staff work actively with these investigators to link them with sites that might make use of their materials.

Recommendation 262 [Vaccine Research and Development ARP Report, p. 51]

HIVNET should participate in expanded Phase II studies of HIV vaccines, especially when such trials involve people at some risk of HIV infection.

Current Status

Plans are currently under way to carry out a joint Phase II vaccine trial in the AVEG and HIVNET. The AVEG and HIVNET investigators met to work on this trial in early November 1996.

Please refer to the NIH response to Recommendation 252.

Recommendation 263 [Vaccine Research and Development ARP Report, p. 51]

Options should be developed to allow individuals to enroll in studies of the clinical benefit of early treatment, especially if the scope of such studies are expanded to include people with documented recent infections who are already antibody positive.

Current Status

NIAID recognized acute infection, early disease, and early therapeutic intervention as some of the most exciting and potentially promising areas of scientific research. NIAID currently supports research in cohorts (WIHS, WITS, HIVNET) that include high-risk HIV-uninfected individuals. NIAID also supports several unsolicited grants (R01s, P01s) and developmental projects (through CFARs) that focus on early infection pathogenesis and treatment.

Future Actions

For FY 1997 and FY 1998, NIAID will establish an Acute Infection and Early Disease Research Network that will specifically support research on new seroconvertors. The purpose of this initiative is to support investigator-initiated research on the pathogenesis of acute infection, immune responses, mechanisms of viral spread during early infection, and outcomes of early therapeutic interventions. Investigators from all cohorts and clinical trials supported by NIAID

have been encouraged to form collaborations and submit applications for the Acute Infection and Early Disease Research Network initiative.

NIAID will continue to support the cohorts and trials networks, including HIVNET, that serve as the patient base for this research. NIAID will fund the highest quality science that addresses issues of acute infection and early disease, through the initiatives in FY 1997 and 1998 and through unsolicited applications.

Recommendation 264 [Vaccine Research and Development ARP Report, p. 51]

> *NIAID should exert closer oversight of HIVNET and the Master Contract mechanisms and initiate regular reevaluation of the funding mechanisms and funding level as changes in vaccine development plans occur.*

Current Status

In June 1996, NIAID and OAR convened a multidisciplinary panel of experts to conduct a review of the HIVNET organization, governance, research, and funding. In the areas of NIAID oversight, the panel recommended the following:

> The management and oversight of HIVNET needs to be more clearly defined, specifically with regard to (1) the roles and responsibilities of HIVNET contractors and DAIDS/ NIAID staff; (2) the process that ensures the highest scientific peer review of HIVNET-sponsored trials; and (3) the availability of specimens to other laboratories conducting related research on vaccine development and on the immunology and virology of HIV infection.

Future Actions

NIAID will continue to fund HIVNET as a master contract because of the flexibility to reduce or expand the number of sites conducting studies. Staff will continue to work with HIVNET investigators to implement the research priorities outlined in the scientific agenda proposed by the investigators and endorsed by the review panel. Special attention will be given to any changes that may occur in vaccine development plans. Recommendations of the panel are being incorporated into the operation of HIVNET. For example, changes in the peer-review process for studies and sites, as provided by HIVNET Master Contractors, will continue with oversight being provided by review staff from NIAID. Where needed, NIAID staff will continue to seek help from OAR in fostering inter-ICD collaboration.

Recommendation 265 [Vaccine Research and Development ARP Report, p. 51]

> *A reasonable percentage of the cost of HIVNET should be coded for clinical vaccine trial preparedness. The rest of the cost must be justified by the strength of the other research*

and coded appropriately under objectives in the annual NIH Plan for HIV-Related Research.

Current Status

NIAID followed OAR guidelines in the coding of vaccine projects, including HIVNET, for FY 1994 (the data evaluated by the Area Review Panel) and agrees that some aspects were confusing. Inherent in currently employed coding schemes for complex, multidisciplinary scientific research (such as AIDS vaccine research) are unavoidable artifacts related to definition of fields and allocation of dollars. Since the FY 1994 coding, there has been greater clarification between OAR and NIAID about what should and should not be included in "vaccine research" according to the NIH Plan for HIV-Related Research. For FY 1995 and FY 1996, only those funds that are spent on vaccine research or preparedness for efficacy trials are coded as "vaccines." Biomedical prevention research is now reported under the "natural history, epidemiology, and prevention" section of the Plan.

Future Actions

NIAID will continue to report its research according to its understanding of the NIH Plan for HIV-Related Research. NIAID also will continue to review and revise its "AIDS-related" guidelines to ensure that they reflect current scientific developments and research priorities.

Recommendation 266 [Vaccine Research and Development ARP Report, p. 51]

Trials of HIV vaccines in the infants born to HIV-infected mothers should be conducted independently of trials in other high-risk populations, because the risk of infection, even with AZT treatment, still exceeds that in most at-risk adult populations.

Current Status and Future Actions

NIAID agrees that trials of vaccines in infants born to HIV-infected mothers should be conducted independently of trials in other populations. Phase I vaccine studies are currently under way within the Pediatric ACTG. The priority of future active and/or passive vaccine studies will need to take into account the availability of vaccine products for infants, while giving consideration to other promising antiretroviral and immunologic interventions that are also currently available for testing in perinatal HIV prevention trials.

Recommendation 267 [Vaccine Research and Development ARP Report, p. 51]

NIAID should explore ways that bring AVEG and HIVNET together that build on the strengths of each group and facilitate sharing of knowledge and skills.

Current Status

NIAID agrees that greater communication between the AVEG and HIVNET is an excellent goal. To that end, the executive committees of the two groups have begun to hold joint meetings. Other efforts include participation of both groups in the annual Advances in HIV Vaccines Conference, sponsored by NIAID, and a joint training session for the AVEG and HIVNET CABs that was funded by the OAR. In addition, there are ongoing plans for AVEG and HIVNET to jointly conduct a Phase II vaccine trial.

Future Actions

NIAID will continue to explore ways to increase communication between the AVEG and HIVNET groups and their community partners.

Recommendation 268 [Vaccine Research and Development ARP Report, p. 51]

> *NIAID should consider if and how its intramural program can contribute to the clinical vaccine development effort. This effort should be coordinated with the extramural AVEG efforts.*

Current Status

NIAID intramural researchers have played an important role in conducting early Phase I trials of innovative vaccine designs. For example, the initial trials of gp160 were conducted within the NIAID intramural clinical program; followup Phase I/II trials in seropositives were then performed through the extramural program. Similarly, early trials of "naked" DNA vaccines are now being conducted within the intramural program with the intent to share the data with the extramural community and AVEG, who would conduct additional Phase I/II trials. Thus, the intramural program provides an additional critical resource for the intensive laboratory and clinical monitoring necessary to conduct Phase I trials of new innovative concepts. In addition, intramural and extramural vaccine investigators meet on a regular basis and share data and reagents.

Future Actions

There will continue to be ongoing discussions and information sharing between the NIAID intramural group and the AVEG. The NIAID intramural program will continue to conduct early stage trials of innovative products in collaboration with extramural AVEG efforts as appropriate.

Recommendation 269 [Vaccine Research and Development ARP Report, p. 51]

As NCI vaccine concepts reach the stage for testing in clinical trials for safety and immunogenicity, every effort should be made to advance them into existing NIAID Phase I/II trial programs to avoid duplication of resources and effort.

Current Status and Future Actions

A Phase I trial of HIV-1 peptide antigens targeted to the generation of cytotoxic T cells has begun. This trial is a collaboration between NCI's Molecular Immunogenetics and Vaccine Research Section and NCI's Medicine Branch that is being conducted in the NIH Clinical Center. Three groups of eight seropositive but asymptomatic patients will be immunized with synthetic peptides in six doses. Only the first eight patients have been recruited and immunized. For this and any future NCI-initiated clinical trials, duplication of resources and effort will be avoided by regular updates to vaccine interest groups in other ICDs and coordination with other AIDS vaccine clinical trials sponsored by NIH.

Recommendation 270 [Vaccine Research and Development ARP Report, p. 52]

NCRR and OAR should work together to develop a mechanism for direct budgeting and tracking of AIDS research funds allocated to vaccine clinical trials.

Current Status

NCRR currently uses the information provided in annual progress reports to track the AIDS research funds allocated to vaccine clinical trials. Subprojects identified in the progress reports are assigned dollars based on calculations using the number of patient days and visits reported for each subproject. The subproject data, however, are from the progress report of the previous fiscal year, which are the most current data available, while the dollars being assigned are from the current fiscal year. There is no mechanism currently available to assign current fiscal year dollars to current fiscal year subprojects because which subprojects are actually done is determined by the GCRC, not by NCRR, and the data on those subprojects are not available to NCRR until the following fiscal year.

Future Actions

NCRR will continue to collect and report data on AIDS research funds allocated to vaccine clinical trials using the current system. There are no clear alternatives to using progress report data in conjunction with current fiscal year data without causing additional and extremely difficult reporting burdens upon grantees. OAR and NCRR will work together to develop approaches for more accurate reporting from the GCRC sites on the level of AIDS clinical research, including vaccine research conducted at these sites.

Recommendation 271 [Vaccine Research and Development ARP Report, p. 52]

A substantial proportion of the budget assigned to AIDS vaccine clinical trials infrastructure and AIDS training requires reexamination. FIC and OAR should work together to ensure that assignment of codes for vaccine clinical trials is appropriately applied.

Current Status

FIC has already taken steps to address this issue. During development of the FY 1997 budget proposals submitted to OAR in FY 1995, an analysis was made of publications from the FIC-sponsored AITRP. FIC subsequently proposed a substantial reallocation of its AIDS budget previously related to vaccines to more accurately reflect the diversity of research training carried out under the program. Under the previous allocation (the one reviewed by the Vaccine Area Review Panel), FIC was shown as devoting approximately 75 percent of the AITRP to vaccines and 25 percent to training. Under the revised allocation, that portion previously allocated exclusively to vaccines was redistributed nearly equally among epidemiology/natural history, etiology and pathogenesis, and vaccines. FIC will continue to monitor changes in the scientific direction of AITRP to ensure that coding reflects current activities and emerging scientific opportunities.

Future Activities

FIC will ensure that future coding will reflect activities across the spectrum of HIV prevention research.

Recommendation 272 [Vaccine Research and Development ARP Report, p. 66]

OAR and NCRR should make AIDS resources available through open, competitive review to investigators who seek to perform "pilot" vaccine studies. NCRR should devise a system to ensure access to animals for AIDS vaccine studies by non-RPRC investigators.

Please refer to the NIH response to Recommendation 36.

Recommendation 273 [Vaccine Research and Development ARP Report, p. 66]

NCRR should work with OAR and research teams studying AIDS vaccine approaches to provide adequate animal resources for testing novel vaccines, both at the RPRCs as well as at other sites.

Current Status

A notice has been published in the *NIH Guide for Grants and Contracts* in January 1997 describing procedures for accessing RPRCs. In the past, each individual RPRC had its own standard procedures by which investigators could request the necessary resources, including laboratory space, support staff, and animals to conduct research on nonhuman primates at the facility. These procedures are now being standardized for all of the RPRCs, and the criteria and policies will be published in the *NIH Guide for Grants and Contracts* as well as on the NCRR homepage.

Future Actions

These standard procedures set up a common mechanism for accessing the RPRC resources and establishing vaccine research protocols.

Recommendation 274 [Vaccine Research and Development ARP Report, p. 66]

NCRR should better coordinate and integrate its HIV/AIDS vaccine research activities with other ICDs to allow better planning for nonhuman primate research resources.

Current Status

The priorities with regard to HIV/AIDS vaccine research in nonhuman primates are primarily the responsibility of the categorical Institutes that serve as the primary funding source for studies for HIV/AIDS vaccine research carried out at the network of primate centers. The RPRCs serve as

hosts only to research already funded by the categorical Institutes and thus do not determine the priorities of research per se.

Future Actions

The NCRR will be informed by its AIDS Advisory Committee on needs related to animal availability, use, and maintenance that have an impact on AIDS research, including vaccine research activities.

Drug Discovery Area Review Panel Recommendations

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BASIC AND APPLIED HIV RESEARCH

Recommendation 275 [Drug Discovery ARP Report, p. 2, No. 1]

Support of basic and applied HIV (and all retroviral) research should be continued.

Please refer to the NIH response to Recommendation 1.

Recommendation 276 [Drug Discovery ARP Report, p. 2, No. 2]

Better communication is required between the Institutes and the OAR and among the specific Institutes involved in the support of basic and applied HIV-related research.

Current Status

Several cross-Institute efforts are ongoing to foster better communication and collaboration in support of basic and applied HIV-related research. Examples include the following:

- NIAID and NCI have a joint working group (NCI Drug Decision Network) for drug discovery and development.
- NIAID and NCI participate in medicinal chemistry collaborations through exchange of information, selective access to chemical databases, and systematic testing of chemical compounds for anti-infective activity.
- *In vitro* and *in vivo* contractual resources (e.g., small animal models efficacy studies; primate/SIV model; specialized *in vitro* confirmatory studies) can be accessed as needed by the different NIH Institutes.
- NIAID Preclinical Therapeutics Development Committee (DPTDC) considers requests to NIAID from extramural sponsors for confirmatory evaluation and subsequent development of promising agents. DPTDC members represent different Government agencies (e.g., NIH, FDA). As indicated above, DPTDC uses testing and development resources from different Institutes and agencies.
- NIAID and NCI have a joint working group for microbicides evaluation and development.
- NIAID coordinates a TB working group that interacts with NHLBI, NIDA, DRG, NINR, and the CDC.
- NIAID coordinates an OI working group with participation by program officers within the Institute, by investigators from the Clinical Center, and by microbiologists from the FDA.

- NIAID can access NCI's drug database and repository for targeted discovery of new therapeutic entities.

- ICDs make extensive use of cosponsored programs (preclinical, clinical, centers) related to two or more ICDs to reach a broader base of investigators, coordinate efforts, and maximize resources. Examples include the following:

NIAID/NIMH/NINDS:	PA for the NCDDG-HIV
NIAID/NCI:	PA for improved preclinical models for drug discovery
NIAID/NIGMS:	PA for structure determination of new viral targets
NIAID/NIMH:	Centers for AIDS Research (CFARs)
NIAID/NIDA/NICHD/NIDR/NCI:	Women's Inter-Agency HIV Study (WIHS)
NIAID/NCI:	Multicenter AIDS Cohort Study (MACS)
NIAID/NICHD:	Women and Infants Transmission Study (WITS)

Future Actions

The OAR will establish a Web page to effectively disseminate information to the scientific community on AIDS research opportunities in the ICDs. This resource will link NIH program staff and facilitate communication with and between Institutes. This central point of contact for investigators should contain pointers to each of the ICDs involved in AIDS research and list resources, program officer contacts, initiatives, and other information essential for improved communications.

The OAR will establish an internal AIDS Interest Group list server for rapid communication and discussion of collaborative efforts among the ICDs.

The NIAID OI Working Group's participation will be expanded to include program officers from other ICDs with interest in OIs, as well as an OAR representative. This will be for the purpose of exchanging information on initiatives and existing portfolios and stimulating discussions of future collaborations. The ICDs involved should include NCI, NHLBI, NIDDK, NIDR, NEI, NIGMS, and others as appropriate.

In addition, please refer to the NIH response to Recommendation 2.

Recommendation 277 [Drug Discovery ARP Report, p. 2, No. 3]

The OAR should develop a system for identifying priority areas for NIH support and for encouraging new basic research activities. This could include the formation of a blue-ribbon panel that would meet at regular intervals to assess the state of the art in HIV basic and applied research and to recommend areas for future or continued focus. This

panel would also consider the likelihood of private sector involvement in various areas of HIV research.

Current Status

NIH and its component ICDs convene panels of non-Government experts from academia, industry, not-for-profit organizations, and community constituency groups to provide advice and guidance for future direction based on their assessment of individual ICD programs and projects. This includes identifying high-priority areas for future research to discover and develop new and improved therapeutics and to translate advances in basic research into advances in clinical research and treatment. These external panels also provide assistance in determining the appropriate allocation of resources to these high-priority areas. Several of the ICD-specific advisory committees and groups that provide this kind of advice and guidance include the following:

- A working group of NCI Board of Scientific Advisors, which is currently reviewing the Developmental Therapeutics Program. The purpose of this review is to assess the existing program and develop recommendations for the future scope and direction for the program.

- NIAID's ARAC and the AIDS subcommittee of the NIAID Advisory Council review the status of HIV/AIDS research and identify those areas that should be developed into program initiatives. The advice of these committees is an integral part of the NIAID planning process.

- NIAID also engages non-Government experts (from the academic, pharmaceutical, and constituency sectors) to review and provide input on its Research Agenda, which is updated yearly and is thus kept current with new findings, high-impact research, and emerging basic and applied research opportunities.

In addition, many of the ICDs collaborate with representatives from the pharmaceutical and biotechnology industries through program-related activities, including the NIGMS structural biology efforts.

Future Actions

NIH acknowledges the need to establish a system for identifying trans-ICD priority areas for supporting and encouraging new basic research activities. NIH recognizes the need to establish on a regular basis an assessment of the state of the science in major areas of AIDS research. To meet these needs, the OARAC should consider convening a periodic scientific workshop (perhaps in conjunction with the annual Conference on Retroviruses and Opportunistic Infections), in addition to ICD-sponsored focused workshops and conferences. The workshop should focus on recent scientific advances and opportunities for research within one of the areas of emphasis in the annual NIH Plan for HIV-Related Research.

A member from OARAC should serve as cochair of the workshop, which should include experts in the designated field of research from academia, industry, professional organizations, and community constituency groups. A summary of the workshop should be presented to the entire OARAC and should highlight future scientific opportunities, direction, and priorities in this area of AIDS research. The OARAC should use these reports to provide advice and guidance to the OAR Director so that their recommendations and priorities can be incorporated, as appropriate, into the development of the annual NIH Plan for HIV-Related Research, into the development of the NIH AIDS research budget, and in the awarding of funds from the OAR Discretionary Fund.

OAR will continue to publicize priority research areas for NIH AIDS support by making the annual NIH Plan available on the World Wide Web so that investigators may be informed of priority areas within the Plan.

Recommendation 278 [Drug Discovery ARP Report, p. 2, No. 4]

Investigator-initiated applications should be strongly encouraged for those areas determined to be critical research priorities. This may be accomplished by inviting key and young investigators who are not currently involved in the designated area of research (or who are involved in allied research areas) to specific workshops.

Please refer to the NIH response to Recommendation 11.

Recommendation 279 [Drug Discovery ARP Report, p. 2, No. 5]

Mechanisms for encouraging the initial evaluation of potential lead discoveries relevant to therapeutics should be developed. ICD staff should play a key role in ensuring appropriate contact between discoverers and potential developers. This might include providing appropriate expertise; establishing contacts, as necessary, with the private sector; ensuring rapid dissemination of new data in appropriate venues; and providing support for proof-of-concept testing in animal models and in clinical trials.

Current Status

NIH utilizes several mechanisms to encourage the evaluation of potential lead discoveries relevant to the development of therapeutic agents.

NIH supports, encourages, and facilitates an extensive network among academic and industry investigators. Recipients of NIH research grants, contracts, and cooperative agreements are responsible under the Bayh-Dole Act of 1980 to effectively and efficiently transfer technology to industry for commercial development. NIH requires notification and disclosure of inventions supported by extramural awards and may provide guidance, when requested, to technology-transfer managers at universities and other awardee organizations. Examples include the following:

- Several NIAID programs, including the NCDDG-HIV and SPIRAT, strongly encourage formal collaboration between academic investigators and the private sector. Several compounds supported under these and other NIAID programs have entered clinical studies (e.g., nonnucleoside reverse transcriptase inhibitors, protease inhibitors, Tat inhibitors, and non-drug-based therapeutic strategies). Several of these drugs are part of currently recommended therapeutic regimens.

- NIAID, through a comprehensive contract-supported discovery and development program, provides support for evaluating potential anti-HIV therapeutics. The drug discovery and development program includes general and specialized confirmatory studies *in vitro*, advanced studies in lentivirus animal models (SCID [severe combined immunodeficiency mouse]-hu/HIV, cat/FIV, macaque/SIV), pharmacology, toxicology, analytical chemistry, and synthesis under good laboratory practices.

NCI supports an extensive array of contract research and FCRDC-based contract and Government researchers to promote screening for novel anti-HIV leads and the transition between discovery and development of potential lead agents. The NCI-funded National Products Repository provides a library of natural compounds.

Future Actions

NIH will continue to identify mechanisms to encourage the evaluation of potential lead compounds and their development as potential therapeutic agents. The establishment of efficient information conduits for recipients of NIH awards to develop plans and sponsor research agreements with the private sector will be facilitated through information on the World Wide Web by the NIH Office of Technology Transfer, Office of Extramural Research, and OAR.

The other ICDs will maintain dialogue and cooperate to ensure that potential therapeutics are evaluated using appropriate resources available to the ICDs and that promising therapeutics are developed for clinical evaluation. Inter-ICD discussions and joint meetings will be continued.

MOLECULAR/STRUCTURAL STUDIES

Recommendation 280 [Drug Discovery ARP Report, p. 3, No. 1]

Continued support of structure-based designs focused on the HIV protease and reverse transcriptase (RT) should be evaluated periodically, given the commercial sector's changing interest in these targets.

Current Status

The annual NIGMS AIDS Structural Biology meeting attracts most of the scientists involved in structural studies of RT. This meeting provides a quick survey of the field.

NCI supports a series of discovery and design efforts directed at HIV protease and RT. Several antiprotease compounds are currently in pharmacology studies; the RT-directed effort has suggested a structural basis for potent RT inhibition; a parallel effort has defined novel chemotypes with anti-RT activity.

- Structural determination studies are primarily supported by NIGMS and NIAID. However, NIAID supports (through investigator-initiated R01s and the NCDDG-HIV program) structural studies that lead to rational drug design. Several NIAID-supported studies have led to structural information and/or determination of key HIV molecules (p24, Vpu, protease, RT). Such findings are critical for developing drugs against new targets and for optimizing the activity of current drugs.

- NIAID and NIGMS have been working closely together to translate molecular/structural findings into applied rational drug design. The two Institutes have co-issued PAs, participated in jointly sponsored meetings, and are involved in constant dialogues aimed at maximizing and capitalizing on findings that can lead to the design and development of new and/or improved therapies.

Future Actions

NIH will continue to monitor its level of support for structure-based designs on HIV proteins. Some lead compounds targeting RT have been offered for license to commercial firms, while others are in an advanced state of preclinical study to optimize oral bioavailability in concert with the originating private-sector firms. Protease inhibitor lead compounds are being optimized for pharmaceutic suitability and activity against mutant (drug-resistant) strains.

Recommendation 281 [Drug Discovery ARP Report, p. 3, No. 2]

Support for new structure-based inhibitor design should focus on HIV integrase and on novel approaches to other targets, such as the CD4 receptor.

Current Status

NIH currently supports structure-based inhibitor design studies on HIV integrase as well as novel approaches to other targets.

NIGMS is funding some research on these targets and is currently considering issuing a RFA to support additional research in this targeted area.

NCI collaborates with NIDDK to discover potential integrase-directed inhibitors. To date, 645 compounds have been provided by NCI to this effort, and 171 compounds vetted by structural criteria have been returned to NCI for testing in the *in vitro* cell-based screen. The potential value of CD4 as a target is being considered by the NCI Working Group.

NIAID funds several grants that study the molecular biology and function of integrase and its potential as a therapeutic target. NIAID is pursuing an aggressive, proactive approach to other emerging therapeutic opportunities as well. Examples include the following:

- A seminar series with key research groups investigating the chemokine/chemokine receptor as related to HIV co-receptor. These sessions serve to identify key areas for additional research; key areas requiring additional support; critical reagents needed; therapeutic strategies to pursue; and structural determinations needed to further this breakthrough in HIV research.

- An aggressive program in HIV accessory proteins (Nef, Vpu, Vpr, Vif) and their cellular cofactors with a specific intent to develop these proteins as new therapeutic targets for therapeutic intervention. This effort includes support of structural studies of these proteins by NIGMS and NIAID for rational drug design.

Future Actions

NIH will continue to support research on structure-based inhibitor designs on HIV integrase and on novel approaches to other HIV targets, e.g., ribonuclease H (RNaseH). The ICDs may periodically issue PAs and RFAs to stimulate additional research in this targeted area. NIH will continue to collaborate with academia and industry on integrase and RNaseH inhibitors and encourage submission of compounds on the basis of a more refined understanding of structural basis for integrase action.

Recommendation 282 [Drug Discovery ARP Report, p. 3, No. 3]

Support should continue for structural studies of HIV envelope glycoproteins, regulatory proteins, response elements, and regulatory protein/response element complexes.

Current Status

NIH currently supports, through a variety of funding mechanisms, structural studies of HIV envelope glycoproteins, regulatory proteins, response elements, and regulatory protein/response element complexes. In addition, the NCI repository contains pure synthetic compound and natural product libraries that are being screened in appropriate structurally based assays of the listed targets.

Future Actions

NIH will more aggressively support investigator-initiated structural studies on HIV envelope glycoproteins, regulatory proteins, cellular factors required for HIV replication, response elements, and regulatory protein/response element complexes. This may require ICDs to use the select pay mechanisms to ensure funding of grants in this research area.

Recommendation 283 [Drug Discovery ARP Report, p. 3, No. 4]

Use of diverse funding mechanisms, including both investigator-initiated grants and targeted initiatives, should continue.

Current Status

NIH uses diverse funding mechanisms, including investigator-initiated grants and targeted initiatives where appropriate, to support structural studies on HIV targets. Investigator-initiated research grants are successful in those areas that are better developed.

NCI has a defined route for forming liaisons with commercial firms and academic centers to screen its libraries in structural-based studies. These include the Open Repository Program, where, under an approved Materials Transfer Agreement, natural product extracts are made available. The development of Cooperative Research and Development Agreements (CRADAs) and licensing arrangements also are used to support structural-based research.

Future Actions

NIH will continue to use diverse funding mechanisms to support structural-based research on HIV. Special initiatives will be needed to encourage the determination of structures for which crystals are not now available.

Recommendation 284 [Drug Discovery ARP Report, p. 3, No. 5]

Enhanced cooperation among ICDs for the coordination of structural studies should be ensured by OAR.

Current Status

NIH utilizes several mechanisms to support cooperation of its structural studies. NIGMS annually convenes the AIDS Structural Biology meeting involving multi-ICD program directors as well as representatives from academia and industry. This meeting enhances communication between NIH and extramural researchers in this field. OAR has recently established a trans-NIH AIDS Interest Group, which through meeting seminars and workshops will provide a forum that will enhance AIDS research including structural biology research.

Future Actions

NIH recognizes that enhanced cooperation among ICDs is necessary for better coordination of structural studies. OAR can further this collaboration through the NIH AIDS Interest Group and its planned workshops and seminars.

In addition, improved communication between ICDs can be facilitated by OAR's establishment of a listserv electronic mail system involving all extramural scientists conducting AIDS-related research. This will permit rapid communication in the development of RFAs and more discussions between trans-ICD program directors.

Encouragement for structural studies supported by NIH should be broad enough to include studies of OIs.

Recommendation 285 [Drug Discovery ARP Report, p. 3, No. 6]

> *A uniform policy should be implemented on the timely deposition and release of structural coordinates determined from NIH-supported studies (including research receiving partial NIH support).*

Current Status

Current PHS policy (*PHS Grants Policy Statement* 8-25, *NIH Guide to Grants and Contracts* Vol. 21, No. 33, Sept. 11, 1992) requires the deposition of coordinates in the Protein Data Bank within 1 year of publication. Compliance can easily be checked on the Protein Data Bank Web page (http://www/pdb.bnl.gov), which not only contains the competed entries but enables a status check on all submitted entries. NIH is required to follow PHS policy in conducting this program.

In the new NIGMS RFA for AIDS Program Projects, this policy is modified to require that the coordinates be available at the time of publication. This policy can be implemented for any specific ICD program. Any blanket change, i.e., for all grants supporting structural studies of AIDS-related proteins, would be subject to the usual Office of Management and Budget procedures.

NCI-funded intramural RT and protease efforts have made their coordinates available for use by extramural investigators in the Brookhaven database as soon as the relevant paper reporting the structural detail is accepted for publication.

Future Actions

NIH will continue to insist on compliance with PHS policy on the timely deposition and release of structural coordinates determined from NIH-supported studies. NIH intramural researchers will similarly comply with the same PHS policy. ICDs should strongly consider a similar release-on-publication policy in a special program.

NIAID DRUG DISCOVERY PROGRAMS

Recommendation 286 [Drug Discovery ARP Report, p. 4, No. 1]

> *The NCDDG-HIV and SPIRAT programs should continue at their current level of support. However, both programs should be evaluated in the near future to assess their productivity and recommend appropriate adjustments, in a manner similar to the review initiated prior to the renewal of the NCDDG program.*

Current Status

NIAID is in fundamental agreement with this recommendation. In September 1996, the ARAC gave concept approval to a plan to combine the solicitation for the current NCDDG-HIV and SPIRAT programs into a single initiative for FY 1998. Previously, the programs were funded through separate solicitations. The NCDDG-HIV program was restricted to preclinical studies. The SPIRAT program required clinical studies of a therapeutic strategy by year 3 of the award. At times, these requirements created artificial barriers in the continuum of discovery and development research. An integrated approach eliminates restrictions on scope or timing of clinical trials and provides maximum flexibility to researchers in designing a research project that is easily translated to clinical trials.

Future Actions

NIAID will continue to work with its ARAC and Advisory Council and to seek input from the research community to develop and refine the NCDDG-HIV and SPIRAT programs to maximize the scientific productivity and flexibility for NIAID investigators.

Recommendation 287 [Drug Discovery ARP Report, p. 4, No. 2]

> *The choice of therapeutic targets for study should be guided by an expert panel, including non-Government investigators, that periodically would assess the state of the art in HIV research. Consideration also should be given to the support of programs designed to investigate therapeutic approaches that do not necessarily advance the technological frontier but may have real potential for improving the current clinical management of HIV disease.*

Current Status

The NIAID Drug Discovery programs utilize advice and guidance from outside experts in selecting which therapeutic agents to develop.

- NIAID's ARAC serves as an expert panel including non-Government scientists. NIAID involves the ARAC early in the development of initiatives (PA, RFA, RFP) as well as in

concept clearance that occurs later in this process. At both points, ARAC members review the status of HIV research and recommend to NIAID which scientific areas should be emphasized. ARAC's input is essential in the development and prioritization of these initiatives and needs. A final funding plan is based on the following factors: the evaluations and recommendations of peer reviews; the priorities of the NIAID Research Agenda; the needs and balance of NIAID's scientific portfolio; and the degree by which the proposed research either fills an identified scientific gap or is likely to be translated into a clinical evaluation. Studies under intense investigation elsewhere (e.g., by the pharmaceutical industry) are excluded. These and other considerations are aimed at maximizing available resources for the discovery and development of new and improved therapies (NCDDG-HIV, with close collaborations with industry) and for the rapid translation of promising therapeutics to pilot clinical evaluation and proof-of-concept (SPIRAT).

- In addition to the ARAC's role in advising NIAID on areas of priority, NIAID, NCI, and other ICDs use non-Government advisors to address specific questions when needed, including those concerning high-impact areas.

- NIAID NCDDG-HIV and SPIRAT programs consider all novel therapeutic strategies. These include new therapeutic targets (RNase, integrase, zinc-binding finger in p7 nucleocapsid, nuclear localization signal required for transport of the preintegration complex to the nucleus in nondividing cells, cellular cofactors required for HIV replication), immune reconstitution, cell-based strategy, and others. All new and improved therapeutic approaches are encouraged at both preclinical and early clinical application.

- The NCDDG-HIV program is constantly fine tuned with respect to responsive studies supported under the program, thus seizing therapeutics opportunities as they emerge.

- Since 1995, and with the maturation of the program, the NCDDG-HIV initiative has been issued as an investigator-initiated PA (instead of an RFA).

- With the ongoing and continuous activities that keep NIH abreast of therapeutic possibilities and high-impact research areas as they emerge, and in the spirit of investigator-initiated research, NIH deems that an additional expert panel is not needed for advice on choosing therapeutic targets.

Future Actions

NIAID will continue to utilize non-Government advisors to guide its therapeutic program and identify potential therapeutic targets. In FY 1997, the SPIRAT initiative also will be issued as an investigator-initiated PA. This transition to an investigator-initiated PA mechanism fosters timely infusion and development of new ideas for therapeutic targets and strategies (see also the NIH response to **Recommendation 279**).

The NCDDG-HIV and SPIRAT initiatives were recently combined to further increase the research flexibility of preclinical and clinical investigators.

Recommendation 288 [Drug Discovery ARP Report, p. 5, No. 3]

Realignment of current study sections to include appropriate expertise to evaluate translational research may be essential for assessment of investigator-initiated preclinical and proof-of-concept clinical studies.

Please refer to the NIH response to Recommendation 8.

Recommendation 289 [Drug Discovery ARP Report, p. 5, No. 4]

The AIDS Research and Reference Reagent Program is a valuable resource. NIH-funded investigators should be actively solicited and encouraged to provide, in a timely fashion, novel reagents to the program for potential use by other researchers.

Current Status

NIH recognizes the valuable resource the NIAID AIDS Research and Reference Reagent Program represents. The AIDS Reagent Program has grown dramatically over its 9-year history. Its 1996 catalog (available in several ways, including through the NIAID home page on the World Wide Web) lists over 900 biologicals and chemicals, a 37-percent increase over 1995; and about 70 percent of these were donated by NIH-funded investigators. More than 1,100 scientific publications have resulted in part from the use of reagents distributed by the AIDS Reagent Program to about 1,500 laboratories in 33 countries.

Requests to donate novel reagents appear in the catalog, in AIDS Reagent Program newsletters distributed two or three times each year to more than 3,000 registered users, and in AIDS Reagent Program flyers distributed at many scientific meetings.

Future Actions

NIH will encourage increased participation in the AIDS Reagent Program.

NIAID and its contractor for the AIDS Reagent Program will continue its effort to disseminate information about the program and seek contributors of reagents.

ANIMAL MODELS

Recommendation 290 [Drug Discovery ARP Report, p. 6, No. 1]

There remains a critical need for further development and optimization of animal models for HIV disease. This need is likely to become increasingly important in the future. Different animal models clearly will be required to meet different research needs. Some models are particularly well-suited for studies of pathogenesis, while others are useful for the preclinical evaluation of new therapeutic agents. It will be particularly important to support the development of a model that can be used for both types of studies.

Recommendation 291 [Drug Discovery ARP Report, p. 6, No. 2]

NIH should strive to optimize and validate the small-animal models (e.g., various mouse and cat models) that currently appear useful for preclinical evaluation of anti-HIV compounds, to determine which (if any) of the models are predictive of efficacy and pharmacodynamic attributes in humans. Those models determined to be relevant and useful should be provided with additional infrastructure and support; support for other models should be de-emphasized.

Recommendation 292 [Drug Discovery ARP Report, p. 6, No. 3]

More resources should be devoted to the development and optimization of the SIV-infected rhesus macaque model for preclinical drug evaluation in vivo*. Additional support would be valuable for further derivation and standardization of molecularly cloned SHIV recombinants, expansion of colony size to reduce animal costs, and infrastructure for housing and research facilities.*

Recommendation 293 [Drug Discovery ARP Report, p. 6, No. 4]

Drug discovery research involving the chimpanzee, rabbit/HIV, and SPF macaque models has not been productive. Funds for this research should be redirected.

Current Status

NIH continues to recognize the critical need for further development of animal models for HIV disease. These models are important for studies on HIV pathogenesis as well as for the evaluation of potential therapeutic agents and vaccine candidates.

NIH supports, through a variety of ICD programs, the development and optimization of several animal models for HIV disease. Examples of such programs include the following:

- NCI has successfully introduced the “hollow fiber” model wherein HIV-infected cells in porous fibers can be inserted in various body compartments to discern pharmacologic features of a new drug. “Hollow fiber activity” at a distant site is now a key feature in prioritizing leads for further development by NCI. Of these, five novel classes of compounds that originated in the pharmaceutical industry have demonstrated activity at

distant body sites from the port of injection. The hollow fiber technique has been demonstrated to be suitable for pharmacologic optimization of potential agents.

- Animal lentivirus models are an integral part of NIAID drug discovery and development programs (see also the NIH response to **Recommendation 279**). These include the SCID-thy/liv (SCID mouse engrafted with human fetal thymus and liver tissues); the rhesus macaque/SIV model; and the cat/FIV model. Through these resources, NIAID provides assistance to sponsors (academic, private sector) of promising agents. Studies in animal models include the following:

  — Efficacy studies (virological and immunological parameters)

  — Monotherapy and combination studies

  — Dose-finding studies

  — Treatment duration studies

  — Chemoprophylaxis studies

  — Limited toxicity and pharmacokinetics studies (NIAID has contract resources dedicated to comprehensive toxicology and pharmacokinetics studies in mice, dogs, and monkeys)

  — Proposed prevention studies with topical microbicides (cat/FIV; monkey/SIV)

- Of the three models cited, the SCID-thy/liv has been used most extensively in first-line efficacy and intragraft pathogenesis studies. Recent improvement in the model allows more extensive virologic studies in the peripheral blood and suggests the possible convergence of efficacy and pathogenesis studies in this model.

- The monkey/SIV model is already used in several kinds of studies, namely, efficacy, treatment regimen, pathogenesis, and chemoprevention.

- The monkey/SIV RFP has recently been recompeted and awards made in September 1996. Highlights of these awards include the following:

  — An additional contract to a total of three primate contracts for therapeutics

  — Specific studies on chemoprevention and topical microbicide inhibition

  — Use of both SIV isolates and SHIV cloned constructs

- NIAID continues its efforts to validate existing models, particularly the cat/FIV model (see below). Other ongoing activities under the current cat/FIV contract include the following:

— Validating the mucosal challenge model

— Identifying the cell types initially infected by FIV and mode of dissemination (histology, electron microscopy, immunology subtyping, *in situ* hybridization, immunofluorescence)

— Delineating the course of disease and cells involved

— Comparing FIV- and HIV-mediated pathogenesis

- Given the limiting information on the molecular biology of FIV, the model is presently used for development of a mucosal challenge model. Advances in the knowledge base on FIV molecular biology, particularly its similarities and differences with HIV, would fill a critical gap in this model and would allow targeted intervention studies against HIV homologue genes/proteins in a relatively economical animal model.

- Efficacy studies at NIAID do not include chimpanzees, rabbits, or specific-pathogen-free (SPF) macaques models.

Future Actions

NIH will continue to support through various funding mechanisms the development and optimization of animal models as valid systems are proposed and deemed scientifically and technically meritorious. To ensure appropriate review of grant and contract applications supporting such programs, reviewers with appropriate expertise will be added to IRGs.

NIAID plans to issue a PA (for FY 1998 funding) on the cat/FIV model to include studies on FIV molecular biology and on the development of the model for evaluations of therapeutics and mucosa-targeted vaccines.

Recommendation 294 [Drug Discovery ARP Report, p. 6, No. 5]

At this time, animal model research is sufficiently mature so that heavily directed research efforts by NIH program staff are inappropriate. Research funded in the future should be subjected to rigorous peer review. This can be facilitated by refocusing current study sections and ensuring that they have appropriate expertise; study section review is preferable to ad hoc *reviews.*

Please refer to NIH response to Recommendation 8.

Recommendation 295 [Drug Discovery ARP Report, p. 6, No. 6]

The NCRR should ensure broad access by qualified investigators to the resources provided by the RPRCs. This may be accomplished by creating independent peer review panels to evaluate proposed research projects by both Center staff and non-Center investigators seeking access to these facilities. The infrastructure for studies that are approved for implementation at a given Center (including the supply, housing, and handling of the animals; obtaining and processing of specimens) should come from the operating budget of that Center. Competitive renewal of the Center grants should include, as a measure of productivity, a description of the Center's peer review process and its success in supporting studies initiated by non-Center investigators.

Please refer to NIH response to Recommendation 36.

Recommendation 296 [Drug Discovery ARP Report, p. 6, No. 7]

Therapeutic agents that have limited effectiveness in patients with advanced HIV infection may be effective around the time of initial infection or in early stages of the disease. More research on both novel and conventional therapies in primate models should focus on these early time points.

Current Status

This is a valid and excellent recommendation. NIAID has begun evaluating several therapeutics in acute and chronic disease models. Indeed, the standard protocol for the SIV model includes treatment during early stages of infection (see the NIH response to **Recommendations 290-293**). NIAID has been evaluating therapeutics in this model for several years.

Future Actions

Similar studies will be conducted with promising therapeutic agents as they are identified.

NCI HIV DRUG DISCOVERY PROGRAM

Recommendation 297 [Drug Discovery ARP Report, p. 7, No. 1]

The DTP should no longer focus primarily on the nonselective antiviral screen.

Recommendation 298 [Drug Discovery ARP Report, p. 7, No. 2]

The DTP management structure should be reviewed, given its apparent inability to enhance the productivity of the AIDS drug discovery effort.

Current Status

The NCI DTP vigorously disagrees with the assertion that it focuses "primarily" on the non-selective antiviral screen. That is only one of several "targeted" or "focused" efforts among a variety of drug discovery efforts supported by DTP. Others have been quite productive. For example, DTP's program in protease inhibitor development, based on the structural features of HIV protease, has identified compounds that have already progressed to preclinical development. Moreover, the results of DTP's program for detecting inhibitors directed at the p7Zn finger where published in *Science* in an article that included coauthors from a major pharmaceutical firm. These efforts, along with DTP-supported research on the structural basis for RT inhibition, were presented to the reviewing subpanel in a detailed fashion; however, they were not in any way reflected in the final considerations of this subpanel. In addition, presentations also were provided on efforts to develop nonnucleoside RT inhibitors, structural approaches to define integrase inhibitors, and novel strategies to optimize nucleoside treatment of pediatric patients. The omission of any apparent consideration of these issues from the final OARAC-approved document is unfortunate.

Future Actions

As discussed in more detail in the NIH response to **Recommendation 29**, NCI will address the Working Group's recommendation by ceasing all screening of natural product extracts for antiviral activity as of January 1, 1997. The screening of pure synthetic and natural product compounds will continue until further discussion of this matter with the DTP Working Group, which will be organized by the NCI Board of Scientific Advisors.

Recommendation 299 [Drug Discovery ARP Report, p. 7, No. 3]

The DTP should use its core resources to support NIH-wide antiretroviral discovery efforts by providing compounds and natural products for various screening endeavors as well as medicinal chemistry, pharmacologic, and toxicologic support as needed. Ongoing review of the DTP AIDS drug discovery program should include assessment of its ability to support the overall NIH drug discovery effort.

Current Status

Through its "Open Repository" Program, NCI DTP has in place a means by which its natural product extracts and open compounds will continue to be made available to responsible investigators from around the world as they have in the past. Academic and industrial institutions, both large and small, have benefited from the receipt of these extracts since the program's inception. DTP extensively supports workers in NCI's Divisions of Basic and Clinical Science by providing compounds and assays. NIAID representatives participate as voting members on Division of Cancer Treatment, Diagnosis, and Centers Decision Network, chaired by the DTP Associate Director, that considers research proposals and commits NCI contract resources in toxicology, medical chemistry, and pharmacology when appropriate. The products of NCI anti-HIV research have in the past been presented to NIAID's AIDS Clinical Drug Development Committee. Again, these facts and processes were clearly presented in written documentation to the reviewing subpanel but were not considered in the final OARAC-approved document.

Recommendation 300 [Drug Discovery ARP Report, p. 8, No. 4]

> *DTP resources also should be used to support the efforts of other ICDs to develop treatments for opportunistic infections (OIs).*

Current Status

In response to the Review Panel's recommendation, the NCI Office of Technology Development published in the *Federal Register* (August 1996) a public notice of its desire to form a CRADA with responsible investigators and commercial firms to screen its collection of open compounds and natural product extracts for novel agents directed against antibiotic resistant microorganisms and other infections of an emerging and opportunistic nature.

Future Actions

The NCI enthusiastically welcomes this opportunity and will support this effort to its fullest extent.

Recommendation 301 [Drug Discovery ARP Report, p. 8, No. 5]

> *An external scientific advisory board should be constituted to provide guidance regarding appropriate DTP support for NIH drug discovery programs. It is not cost-effective to reproduce the considerable DTP infrastructure in other ICDs.*

Recommendation 302 [Drug Discovery ARP Report, p. 8, No. 6]

> *The operational logistics of the DTP require review and restructuring. Given the Panel's recommendations, a substantial decrease in the size and funding of the DTP's current HIV drug discovery effort may be appropriate.*

Current Status

NCI is pleased to consider continuing advice on the proper scope and direction of its AIDS drug development program. The precise place of such a body within the DTP organization will be determined in consultation with the DTP Working Group, to be convened by NCI'S Board of Scientific Advisors. An additional activity of this group will be to consider DTP operational logistics. The cessation of screening of the natural product extracts will allow a redirection of approximately $1,512,000 of AIDS-related resources.

Recommendation 303 [Drug Discovery ARP Report, p. 8, No. 7]

Support is needed for research on developmental therapeutics for HIV-associated malignancies.

Current Status

NCI DTP has supported the development of novel therapeutics for HIV-associated malignancies. DTP conducted the investigational new drug (IND)-enabling studies for TNP470, of interest as potentially useful in the treatment of KS. DTP has had in place an active screening program for agents directed against AIDS-related lymphoma using a panel of cell lines that included two cell lines derived from patients with AIDS-related lymphoma along with four non-AIDS-related lymphoma cell lines for comparison and using an *in vivo* evaluation in the AS283 model, which was developed from a tumor derived from a patient with AIDS-related lymphoma. Through June 1996, 5,213 compounds had been screened, 164 were referred for *in vivo* evaluation, and 118 were actually tested *in vivo*. Active agents identified include six benzoylphenylureas (a novel chemotype selected for advanced development based on the following features: oral bioavailability, antitubulin activity without providing a substratum for the multidrug resistance transporter), two verrucarins, four rapamycins, dolastatin 10, and flavopiridol. The last two compounds are in clinical trials.

Future Actions

Whether operation of this particular screen should be continued will be considered by the DTP Working Group, and its final evaluation will depend, in part, on the results of initial clinical studies with the agents already selected.

Recommendation 304 [Drug Discovery ARP Report, p. 8]

Support for the NCDDG-OI program should continue at the present level.

Current Status

NIAID welcomes the endorsement of the NCDDG-OI program as an integral part of its drug discovery/development portfolio. In the NIAID HIV/AIDS Research Agenda, NIAID lists the factors that underlie the ICD efforts in drug discovery and development for the OIs. In addition, the variables that are considered in developing a composite research agenda for priorities in OI research include the following:

- Estimated incidence of each OI and its morbidity and mortality
- Implications of the disease for general public health
- Number of available and effective therapies for first-line use as well as alternatives in the setting of relapse or resistance
- Toxicities of available therapeutic interventions
- General need for safer and more effective, long-term prophylaxis
- Level of private-sector interest in drug discovery
- Potential new drugs or vaccines in the development pipeline

Within the past 2 years, NIAID has moved toward increased use of PAs to stimulate investigator-initiated research in all areas of research, including OI studies (NIAID believes that this field in particular will benefit from the ability of investigators to choose a funding mechanism that best suits their research program). To determine which areas of research need stimulation, NIAID regularly assesses the currently funded grant portfolio in the context of the scientific priorities listed in the NIAID HIV/AIDS Research Agenda; gaps identified in the portfolio may be developed into specific initiatives which are reviewed by the NIAID Advisory Council and the ARAC.

In the case of OIs, various forums are also used to identify and develop priorities, e.g., the annual NCDDG-OI meeting of grantees and contractors, meetings of the NIAID OI working group (consisting of staff from DAIDS, Division of Microbiology and Infectious Diseases [DMID], FDA), and NIAID-sponsored scientific meetings and workshops. These groups also advise NIAID on the relative priority of the pathogens. Given the high level of participation of non-Government scientists in the formulation of its OI research agenda (through the ARAC and the various scientific workshops), NIAID does not think that an additional external advisory group

would be useful in determining which organisms should be studied. NIAID will continue to use the various forums to identify gaps in its OI research portfolio and develop initiatives to stimulate research in these areas.

Recommendation 305 [Drug Discovery ARP Report, p. 8, No. 2]

> *Even though it may be anticipated that some pharmaceutical industry support of mycobacterial research will be forthcoming, the present medical need justifies at least short-term support by NIH. However, NIAID should continue to monitor the development of new therapies (especially for* M. avium *complex) by the private sector, with the goal of redirecting funds at the appropriate time.*

Current Status

NIAID maintains an active program in *M. tuberculosis* and *M. avium* research, including drug discovery through R01s and the NCDDG-OI program, chemical screening based on structure-activity relationships, literature surveillance, cell-based assays, and animal-model testing.

Ongoing programs in this area include PA 94-095 "Drug Discovery for Opportunistic Infections Associated with AIDS," which encourages R01 applications related to drugs for *M. avium*, and a drug-screening/animal-model efficacy contract undergoing recompetition for award in FY 1997.

Future Actions

NIAID will continue to monitor the development of new therapies, particularly for disseminated *M. avium* disease, by the private sector. Program staff regularly interact with investigators in the pharmaceutical industry at scientific meetings, monitor patent applications and the published literature, meet regularly with colleagues at the FDA, and discuss the changing industrial involvement with members of the NIAID advisory committees and councils.

Recommendation 306 [Drug Discovery ARP Report, p. 9, No. 3]

> *Support for* Microsporidia, Cryptosporidium, *JC virus, and other pathogens that have less attractive market potential should be emphasized. In general, when projecting future needs, NIH should consider where pharmaceutical industry efforts are being placed, so that Federal funds can be used to target understudied pathogens.*

Current Status

NIH includes the above-named opportunistic pathogens as priorities in the NIH Plan for HIV Related Research and the NIAID HIV/AIDS Research Agenda. These priorities for research emphasis are based on the number of active anti-infectives in the development pipeline by the pharmaceutical industry, on the number of licensed antimicrobials with efficacy against each OI,

the rate of resistance development to standard therapy, the morbidity and mortality of each infection (including effects on quality of life), the incidence of infection throughout the course of HIV infection, the relative number of research grants within the NIH portfolio, and the current state-of-the-art in tissue culture and knowledge regarding the pathophysiology of each infection.

Future Actions

NIH will continue to maintain surveillance to identify in a timely manner emerging opportunities or problems, including outbreaks and development of antimicrobial resistance. With advice from the OARAC, NIAID Advisory Council, and ARAC, OAR and NIAID will assess the need to increase or decrease effort when gaps in and among Government, academic, and industrial programs are identified.

Support for new drug discovery and development efforts related to treatments for infections caused by these organisms will continue to be provided through the SBIR program, the NCDDG-OI program, and appropriate PAs.

In FY 1997, NIAID will give special consideration to applications received in response to PA-96-068 "Innovative Drug Discovery Research in AIDS Opportunistic Infections," which encourages research on human cytomegalovirus, JC virus, *M. avium*, *Pneumocystis carinii*, *Cryptosporidium parvum*, the Microsporida, and *Cryptococcus neoformans.*

Recommendation 307 [Drug Discovery ARP Report, p. 9, No. 4]

The selection of organisms to be studied by the NCDDG system should involve several factors, including the number of Research Project Grants (RPGs) funding research on that organism, its relative importance in the clinical management of AIDS patients, and the commitment of pharmaceutical companies to research on the organism. An external advisory group could significantly assist in determining which organisms should be studied.

Please refer to the NIH response to Recommendation 304.

Recommendation 308 [Drug Discovery ARP Report, p. 9, No. 5]

The NIAID should be encouraged to periodically assess the overall value of individual contracts supporting OI research with respect to productivity, reliability, and user accessibility.

Current Status

There are several mechanisms already in place that are used to periodically assess the overall value of contracts supporting OI research. NIAID believes that current practices provide a rigorous assessment of its OI contract portfolio on a regular basis.

- The portfolio of contracts that support animal testing of potential therapies for AIDS-associated OIs is recompeted every 5 years. Prior to that time, the need for a continued effort on a specific pathogen is evaluated using various criteria and forums listed above (in the NIH response to **Recommendation 304**). During the past several years, there have been major shifts in the OI contract portfolio to reflect changes in priorities. For example, testing on *Pneumocystis* and *Candida* have been scaled back or eliminated because of decreased need. Initiatives for testing therapies against TB, *Cryptosporidium*, and *Histoplasma* have been added as the need has become more pressing.

- All initiatives, including OI testing contracts, are reviewed by the AIDS subcommittee of the ARAC. This group is made up of experts in the fields of AIDS and infectious disease basic and clinical research. As part of their review of each initiative, this group considers the contribution of the initiative to the overall research program, the productivity and usefulness of the current contracts, the continuing need for such a resource, and accessibility to the research community.

- All contract proposals in response to a research initiative, such as the OI testing contracts, undergo peer review. This review includes an evaluation of the scientific merit of the proposed types of studies, the productivity of the group, and the reliability of the information that would be produced.

As in all areas of research, NIAID employs contractors only when specific services or products are being procured. More detail is provided in the response to **Recommendation 238**.

Clinical Trials Area Review Panel Recommendations

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Recommendation 309 [Clinical Trials ARP Report, p. 4, No. 1]

Create a clinical trials coordinating group with broad scientific and community representation, including representatives of ICDs that conduct clinical trials, to coordinate and facilitate inter-Institute collaboration.

This advisory body would be the responsibility of the Office of AIDS Research (OAR) Coordinating Chair for Therapeutics and would report to the Director of the OAR. Other critical functions would include the responsibility to define an overall mission statement for NIH-sponsored therapeutics research, to eliminate redundancy among the various NIH trials programs, and to continually evaluate the appropriate magnitude of the entire clinical trials effort. The focus of this group would be on strategic decisions rather than on operational details or a protocol-by-protocol review.

Please refer to the NIH response to Recommendation 28.

Recommendation 310 [Clinical Trials ARP Report, p. 5, No. 2]

Create a single adult clinical trials network to replace the separate ACTG, CPCRA, DATRI (and possibly SPIRAT) programs under the auspices of the NIAID.

This trials network is envisioned as one that would exhibit extraordinary flexibility, sound scientific leadership, and a range of clinical research capabilities to meet the future challenges of therapeutics research. The use of more than one funding mechanism for support of different elements of the network should provide maximum flexibility.

Please refer to the NIH response to Recommendation 25.

Recommendation 311 [Clinical Trials ARP Report, p. 7, No. 3]

A standard for databases for all NIH-funded HIV/AIDS clinical trials should be developed that would allow for cross-study analyses and longitudinal followup of participants.

Please refer to the NIH response to Recommendation 26.

Recommendation 312 [Clinical Trials ARP Report, p. 8, No. 4]

In general, all ICDs involved in HIV/AIDS clinical trials research should fully utilize and support the single NIAID-sponsored trials network described above. Each relevant ICD should contribute both scientific guidance within its area of expertise and funding

support for the conduct of Phase II-IV trials rather than create anew the capacity to conduct such studies independently.

Please refer to the NIH response to Recommendation 25.

Recommendation 313 [Clinical Trials ARP Report, p. 8, No. 4a]

Future SOCA/ACTG collaborative studies should be developed that consider the other systemic manifestations of CMV disease, the potential interactions between CMV and HIV and their effect on both CMV and HIV disease progression, the antiretroviral effects of some CMV therapies, and the effect of anti-CMV therapy on CMV viral load and the development of resistance. This requires NEI support for a fully collegial interaction between the ophthalmology and infectious disease investigators.

Current Status

The collaboration between SOCA (NEI) and ACTG (NIAID) is a critical one for developing new and effective therapies for the treatment of cytomegalovirus (CMV) retinitis, a devastating complication of patients with advanced AIDS. With new technologies for measuring both HIV and CMV viral load and development of resistance to antiviral therapies, new opportunities exist to better understand the interactions between CMV and HIV and their impact on both CMV and HIV disease progression. These important questions regarding the pathogenesis of CMV and HIV are identified in the FY 1998 NIH Plan for HIV-Related Research, the NIAID HIV/AIDS Research Agenda, and the ACTG Research Agenda and can and should be addressed within the context of SOCA/ACTG collaborative trials.

Future Actions

NEI and NIAID will develop clinical protocols that will further enhance a comprehensive evaluation of systemic manifestions of CMV disease and the potential interaction between CMV and HIV. Interactions among ophthalmic and infectious disease investigators at all stages of protocol development and conduct of the trial will be enhanced through the establishment of a CMV/viral pathogen study group within the AACTG Complications Research Agenda Committee. This new group will replace separate research/protocol development committees within SOCA and ACTG. Studies specifically addressing complex management issues of other CMV end-organ disease may be best accomplished through other collaborations (e.g., ACTG and NARC/NINDS).

SOCA will have the responsibility for providing scientific leadership and day-to-day management oversight of all extramural NIH Phase II/III trials of new treatments for CMV retinitis. NEI will continue to provide direct support for the activities of the SOCA Coordinating Center, Fundus Photograph Reading Center, and Study Chair's office. Maximum use will be made of the ACTG infrastructure to support clinical trial activities at participating ACTG-affiliated clinics and to

support the conduct of sophisticated laboratory assays. The feasibility of using ACTG contractors for site visits and clinic monitoring for SOCA/ACTG clinical trials will be explored. This may be a cost-effective approach and could promote greater consistency across trials. Where appropriate, industry support of the SOCA/ACTG clinical trials will be encouraged, and industry funds, allocated on a per-patient basis, will be used to offset costs to the Federal Government.

Recommendation 314 [Clinical Trials ARP Report, p. 8, No. 4b]

> *The role of and level of support from NINDS for clinical trials of therapy for the neurologic manifestations of HIV/AIDS, as well as for evaluation of possible neurotoxicity, has been inadequate. The commitment of NINDS to such clinical trials should be addressed by the Institute Director.*

Current Status

NINDS continues to be very concerned about the AIDS epidemic and the disorders of the neuromuscular system produced by HIV and opportunistic infectious agents. The NINDS-supported AIDS grant portfolio reflects maturation of neuro-AIDS research over the past decade: from descriptive neuropathology, through the studies of natural history of neurological complications of HIV infection, to clinical studies. The Institute has been working closely with the neuro-AIDS community to promote high-quality clinical trials on potential therapies for neuro-AIDS and its complications. The community of neuro-AIDS investigators has worked for years within the framework provided by the ACTG to investigate treatments for patients with neurological complications. There are neurology components in many of the ACTUs. The NARC was formed to organize these efforts and to promote interactions.

NINDS' major clinical trials program is a product of NARC. It is supported through a program project grant (P01) to Washington University School of Medicine at St. Louis with subcontracting arrangements for neuro-AIDS studies at many ACTUs. Of five clinical trials recommended for funding, three have closed, and two continue.

Future Actions

An award of FY 1996 OAR Discretionary Funds provided a supplement that permitted the NARC community to move ahead and plan a renewal application. The competing renewal application was reviewed and approved by the NINDS Advisory Council in February 1997. NINDS organized a recent workshop, "The NINDS HIV Therapies Workshop," where ideas for possible new therapies were discussed as part of sessions on progressive multifocal leukoencephalopathy, opportunistic viruses, and AIDS dementia. The NINDS program staff spoke at another recent workshop organized by NIMH, and they reiterated the Institute's commitment to the endeavors of these investigators. Several new projects for the NARC Clinical Trial program have emerged, both from the workshops and the annual neuro-AIDS meetings of NARC, and these new projects are parts of the recently renewed NARC program. NINDS will continue to work with these investigators, who more or less constitute the entire neuro-AIDS clinical community; NINDS has

every expectation that the recent resubmission of the clinical trial program will be strong and that it will go on to be funded.

In addition, NINDS will continue to actively seek new grant applications on the treatment of neurological complications of HIV infection in adults and children and will issue PAs in FY 1997 and FY 1998 calling specifically for clinical studies on neuro-AIDS. There are several other smaller clinical studies which NINDS currently supports and two new applications dealing with viral load and imaging in AIDS dementia that appear promising.

Recommendation 315 [Clinical Trials ARP Report, p. 9, No. 4c]

NCI support of extramural trials has been limited to date. The recent initiative that created the AIDS Malignancy Consortium (AMC) in 1995 for the exploration of innovative Phase I/II pilot studies is underfunded. Although additional support for HIV virologic and immunologic testing has been promised by NCI, it remains to be seen whether this is a viable Phase I/IIA research program at the current level of funding. Innovative therapeutic approaches that emerge from this program will require large randomized comparative trials for confirmation. With additional fiscal and scientific support from NCI, Phase IIB/III studies could be performed in the proposed adult trials network.

Alternatively, comparative trials could be conducted in the COGs. However, the potential disadvantage of this approach is that these groups do not have the infectious disease expertise necessary for trial design and for integrated clinical management of HIV-related disease manifestations during the study.

Current Status

Before 1992, the majority of AIDS oncology trials were developed and sponsored by NIAID and primarily focused on antiretroviral therapy and OIs. After joint discussions between NCI and NIAID beginning in October 1992, it was agreed that the scientific leadership and coordination of future trials in NCI would be based in the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment, Diagnosis, and Centers. The existing 12 NCI-funded AIDS Lymphoma Network sites, the NCI Clinical Trials Cooperative Groups, and the NIAID ACTG began to coordinate their work on laboratory correlates and clinical trials.

In 1993, the spectrum of malignancies in AIDS was expanded beyond lymphomas to include cervical cancer, anogenital dysplasia, NHL, and KS through the NCI funding of 11 investigators with R03 small grants. Therapeutic interventions ranged from cytotoxic chemotherapy, biologic therapeutics, to immune-based therapy with CTL directed against viral targets. Some of these trials were conducted in the NCI Clinical Trials Cooperative Groups. Although these efforts produced some forward movement, further coordination between investigators was needed to prioritize research ideas, facilitate clinical trials, and expedite patient accrual.

In 1995, NCI funded the AMC, consisting of 14 investigators with separate U01s at a level of $2.7 million per year for 4 years, to explore hypothesis-based early phase clinical trials. In November 1995, the NCI sponsored the first meeting of this newly formed consortium, including leadership from both NIAID and NCI, investigators from the recently NCI-funded AIDS Malignancy Bank (AMB), and the AMC grantees. A major focus of the meeting was a discussion of potential interactions that would provide complementary research resources, as well as a discussion of the research agenda for the AMC. In February 1996, CTEP obtained a $2.0 million supplement to the existing AMC grants divided as follows: $1.0 million for the Operations, Data Management, and Statistical Center Discretionary Fund to support the laboratory correlative studies and $1.0 million to be divided equally among the 13 clinical trials members to supplement infrastructure needs (e.g., data management, nursing, additional sites).

Three AMC clinical trials are now CTEP-approved and ready for activation, including an intergroup study developed and coordinated by the NCI Clinical Trials Cooperative Group. Three additional AMC clinical trials are in review at CTEP. Several of the virologic and immunologic laboratory studies will be performed by the ACTG core laboratories. There is an active liaison between the AMC investigators and the ACTG Virology and Immunology Core Laboratory investigators as well as with the ACTG Executive Committee.

The NCI Clinical Trials Cooperative Groups have received set-aside funding to perform AIDS malignancy clinical research since 1994, and in FY 1996 these groups received $1.2 million. They have active clinical trials for children, men, and women with AIDS malignancies, including NHL, primary CNS lymphoma, cervical cancer, and KS. The Cooperative Group Chairs participated in a joint, NCI-sponsored meeting of the AMC and AMB at the American Society of Clinical Oncology Meeting in May 1996 to discuss research resources and the potential for intergroup or complementary research agendas. A second NCI-sponsored meeting of these three separately funded groups was held in November 1996 to further these discussions and assess interval progress.

Future Actions

NCI strongly supports the research studies in AIDS malignancies and is providing scientific leadership, developing an AIDS-malignancy research infrastructure, promoting collaborative intergroup research, and incrementally building the necessary financial support. The NCI Clinical Trials Cooperative Groups have demonstrated their interest in and capability of performing clinical trials in AIDS malignancies and will play an increasingly important role as larger trials are needed. The Cooperative Groups' extensive experience with the treatment of leukemia and lymphoma, including a high degree of expertise in managing the infectious complications of immunocompromised cancer patients, will augment the ongoing collaborations with the ACTG to ensure a high-quality resource for confirmatory clinical trials.

Recommendation 316 [Clinical Trials ARP Report, p. 9, No. 4d]

NIMH should be encouraged to support exploratory trials for the treatment of neurocognitive and psychiatric disorders in adults and children. In the future,

comparative studies in adults should be conducted by the proposed integrated network with specific scientific and fiscal support from the NIMH.

Current Status

NIMH is supporting a serodated cohort study at one of its AIDS Research Centers that is yielding important data on the neurocognitive and psychiatric disorders experienced in adults. Neuropsychological, neuropsychiatric, neurological, and neuroimaging data that have been collected every 6 months are being analyzed. These data will form the basis of future treatment studies.

NIMH is currently funding several small trials of medications in neuropsychiatric complications of HIV (e.g., fluoxetine in depressed HIV-infected patients, stimulants for fatigue, testosterone for anergia and mood dysfunction). NIMH also is supporting a large trial of memantine in HIV dementia through the ACTG/NARC network (the study is organized by NIAID and NIMH, which is cofunding the neuropsychiatric component). In addition, NIMH has organized expert scientists to layout research directions in the area of neuropsychopharmacology of HIV/AIDS that will be used to stimulate new research.

Future Actions

Neuropsychiatric sequelae (e.g., severe depression, anxiety) are a major concern for persons with HIV disease. As part of the effort to mitigate the effects of these disorders, NIMH will implement this recommendation by identifying the cofactors on which it may be possible to intervene. NIMH also will take the lead in supporting research to assess the effectiveness of interventions aimed at treating psychiatric conditions, promoting healthy behaviors, maintaining impulse control and good judgment, and maintaining low-risk HIV-related sexual behaviors.

Another strategy that NIMH will continue to pursue is to make presentations at scientific conferences in order to inform scientists of the research potential in the mental health aspects of HIV infection. NIMH will identify research that can be supplemented to yield critical neurocognitive and psychiatric data for HIV/AIDS patients.

NIMH, in collaboration with other ICDs, will implement a research initiative to examine the effects of antiretroviral treatments on cognitive impairment. Incorporating a neurocognitive and psychiatric assessment component into larger ongoing antiretroviral trials will be more cost-effective than performing smaller separate ones. Because it is not known whether these agents penetrate the CNS, this treatment may not translate into improved neurobehavioral outcomes. Preliminary data may provide insight on the potential impact of antiretrovirals on neurocognitive functioning. By decreasing the systemic viral load, the life span of the individual may potentially be increased.

In collaboration with NICHD and NIAID, NIMH is taking the lead in the development of a neuropsychological and neurological battery that can be used in neurodevelopmental research

with infants and children. When the reliability and validity of this assessment strategy have been established, NIMH will implement this recommendation by encouraging the use of this battery that will permit studying neurocognitive constructs across the age span.

Recommendation 317 [Clinical Trials ARP Report, p. 9, No. 4e]

> *Every effort should be made to avoid competition and redundancy between the intramural and extramural programs. The intramural trials efforts should capitalize on the unique capabilities of the NIH Clinical Center and on the specific expertise of the sponsoring ICD. The Clinical Center provides the opportunity to bring patients to a single center for clinical investigation at no cost, including travel expenses, to the trial participants. This level of patient support is not routinely available even at excellent university medical centers with NIH-funded General Clinical Research Centers (GCRCs).*

Current Status

Since the Task Force review in the fall of 1995, there has been feedback from an independent outside review of the role of the Clinical Center (the "Smits Committee"), and a decision has been made to proceed with building a new NIH Clinical Center. Overall, there has been a consensus that the NIH Clinical Center offers a unique resource to conduct clinical research. In response to the Bishop-Calabresi report, the NCI's intramural program has been reorganized: the clinical research of that Institute is now conducted within a newly formed Division of Clinical Sciences, and an HIV and AIDS Malignancy Branch has been formed within this division that is responsible for conducting the adult and pediatric clinical trials. Intramural clinical researchers in all Institutes have endeavored to reduce redundancy with extramural trials. Semiannual "intergroup" meetings have recently been initiated in order to increase communication and reduce redundancy in the whole NIH portfolio of AIDS clinical trials, and intramural clinical researchers have participated in this process.

Future Actions

NIH agrees that the intramural trials effort should capitalize on the unique capabilities of the Clinical Center and that redundancy between the intramural and extramural clinical trials effort should be avoided whenever possible. These goals will be achieved in part by encouraging discussions between intramural and extramural investigators (which is already occurring through various mechanisms, including the membership of intramural investigators on ACTG scientific committees). Intramural clinical researchers also will participate in the semiannual OAR Coordinating Committee on Therapeutics and NIAID Inter-Group Scientific Leadership meetings. The clinical research portfolio of the NIAID is now reviewed annually by the Office on Clinical Research. Most intramural trials in NCI also are reviewed on an ongoing basis to avoid duplication of effort with the extramural community effort. Intramural laboratories in the Institutes are reviewed every 4 years by the Boards of Scientific Councilors, and these reviews will ensure that resources are being used in a way that is consistent with the strengths of their ICDs and the opportunities provided by the Clinical Center.

Recommendation 318 [Clinical Trials ARP Report, p. 9, No. 5]

The Panel recommends that Institutes with a disease-specific (e.g., NCI) or an organ system-specific focus (e.g., NEI, NINDS, NIDDK) be responsible scientifically and fiscally for clinical trials specific to their mandate. Scientific priorities and consequent funding of the various intramural clinical trials efforts should be carefully scrutinized by each Institute Director.

The Panel carefully considered funding for NIH clinical trials, including both intramural and extramural programs. The need for a coordinated approach to extramural clinical trials is described above. While each Institute should define its own commitment to an intramural clinical trials effort, intramural trials should be designed to optimally exploit the unique resources of the NIH Clinical Center. Trials that do not take advantage of these resources and are redundant with extramural and pharmaceutical efforts should be avoided.

Please refer to the NIH response to Recommendation 13.

Recommendation 319 [Clinical Trials ARP Report, p. 10, No. 6]

The Panel unequivocally supports the need for greater balance between investigator-initiated grants and targeted initiatives for support of clinical trials. Small-scale trials can and should be supported by individual grants.

This may require realignment of existing study sections to provide sufficient expertise for adequate review of such applications. Nonetheless, the Panel realizes that development of an adequate infrastructure for larger trials networks is crucial and will continue to require the allocation of targeted funds.

Recommendation 320 [Clinical Trials ARP Report, p. 10, No. 7]

Adequate and appropriate scientific review of proposed clinical trials programs—regardless of funding mechanism—must involve the most qualified, knowledgeable scientists.

Consideration should be given to the realignment of existing study sections that could be supplemented by an expert panel with defined terms of membership for the review of clinical trials networks, rather than the current ad hoc *reviews assembled by the ICDs which may not have the requisite expertise. Increased inclusion of experienced HIV clinical trialists from outside the United States may be especially helpful when the majority of experienced U.S. investigators are also applicants.*

Current Status

NIH supports efforts to address the need for greater balance between investigator-initiated grants and targeted initiatives for support of clinical trials. Small-scale pilot trials can and should be

supported by individual grants. The NIH acknowledges that adequate and appropriate scientific review of proposed clinical trials programs must involve the most qualified, knowledgeable scientists. One of the biggest challenges in developing expert panel review groups is the identification of experienced HIV clinical trialists who do not have a potential conflict of interest involving the review of a particular clinical trials program, particularly when the majority of experienced U.S. investigators are also applicants. Current experience in the development of the review committee for the PACTG RFAs reveals that superb, experienced reviewers can be identified, both from the United States and abroad.

Currently, clinical trial networks are for the most part reviewed by ICD committees. Investigator-initiated clinical trials that are not part of networks or cooperative groups are sometimes reviewed, depending on individual ICD policies, in DRG study sections. When this happens, if appropriate expertise for all aspects of the application is not on the study section, additional reviewers are invited to participate. Many of these additional reviewers ultimately become study section members.

NCI has spent extensive time in selecting review panels for its clinical trials programs. Peer review for the RFA-targeted applications draws upon an excellent cadre of investigators from multiple disciplines, and the quality of the research and personnel at the chosen sites ranged from outstanding to excellent. As noted above, the success rate for non-RFA NCI-assigned AIDS grant applications reviewed through the DRG ranged from 20 percent to 45.5 percent over the last three grant application cycles.

In 1992, NCI recognized the need to stimulate research in the area of AIDS malignancies as this research area seemed to “fall through the cracks” of the research agendas of the currently existing NIH-funded clinical trials cooperative groups. Coordination and prioritization of clinical research in AIDS malignancies through development of adequate infrastructure was determined to be essential, and this need was the basis for developing both the AMC and the AMB. The research is being carefully coordinated with the existing NCI Clinical Trials Cooperative Groups. In addition, the virology and immunology expertise of the NIAID-funded investigators is also being utilized. Investigator-initiated research will continue to be a high-priority for the Institute.

In reviewing the success rate for the last three cycles of non-RFA DRG-reviewed applications in AIDS, approximately 6.5 to 10 percent of the 250 AIDS applications were assigned to NCI. Of those 6.5 to 10 percent assigned to NCI, the success rates for grant funding ranged from 20 to 45.5 percent. This rate is comparable to the success rate for non-AIDS-related cancer grants at the NCI.

NICHD currently supports several perinatal HIV transmission prevention trials via the R01 mechanism, including a trial evaluating a shortened ACTG 076-type regimen in Thailand, two studies evaluating different regimens of maternal seropositive and seronegative newborn vitamin A supplementation in Africa, and a study of breast versus bottle-feeding in Kenya.

A recent NIAID PA (PA-96-069) specifically encourages application for funding small-scale trials for initial setting of novel and innovative concepts.

Future Actions

NIH will continue to support clinical trials through a variety of funding mechanisms including the support of small-scale clinical trials through individual grants, particularly for the initial testing of novel and innovative concepts.

NIH will continue its ongoing policy to add *ad hoc* members to existing DRG study sections and use special emphasis panels to ensure appropriate scientific expertise on study sections. This will include using clinical trialists from both the United States and abroad to provide the necessary expertise to review grant applications.

In addition, please refer to the NIH responses to Recommendations 7 and 8.

Recommendation 321 [Clinical Trials ARP Report, p. 10, No. 8]

NIH and industry efforts should be coordinated. NIH studies should be undertaken that extend our knowledge of disease processes as well as assess the impact of therapy, which is typically not the focus of industry-sponsored trials.

A distinction should be made between studies that would be performed by the pharmaceutical industry irrespective of the existence of an NIH clinical trials network and studies of greater scientific and medical relevance, such as trials to define optimal patient management for some aspect of HIV disease and trials to evaluate different therapeutic strategies. Cost-sharing arrangements with industry should be encouraged for the performance of collaborative studies.

Current Status

NIH agrees with the importance of coordinating the efforts of NIH and the pharmaceutical industry. The focus of NIH-supported clinical research should be studies that extend the knowledge of disease processes as well as assess the impact of therapy—areas that are not typically the focus of industry-sponsored trials. It is important that NIH should not duplicate industry efforts. In addition, because of the growing costs of performing clinical studies, particularly those laden with complex and expensive laboratory evaluations or extraordinary patient evaluations, cost-sharing arrangements with industry are becoming an increasingly common way to implement collaborative studies between NIH and industry.

NIAID and NCI have a long history of collaboration with the pharmaceutical industry in the design and conduct of clinical trials. It is recognized that the endpoints for industry-sponsored trials (e.g., a new drug application) and for ICD-sponsored trials (e.g., finding the optimum therapy or understanding better the underlying pathology of a particular disease) may be different, but it is understood that both efforts ultimately are directed to bringing effective therapies into the marketplace. Cost-sharing arrangements with industry are already available through Clinical Trials Agreements (CTAs) and CRADAs.

Future Actions

NIH agrees with the recommendation and will further continue its efforts in collaborating with the pharmaceutical industry in the design and conduct of clinical trials. NIH will continue to use CTAs and CRADAs in interactions with the pharmaceutical industry in the conduct of clinical trials. Cost-sharing arrangements will continue to be used in the conduct of these trials with industry.

Recommendation 322 [Clinical Trials ARP Report, p. 11, No. 9]

> *The Panel did not dissect in detail the scientific agenda of each clinical trials program. These issues have been the subject of other targeted reviews. However, the Panel did recognize cross-cutting areas that should be of high priority. These include: (1) validation of surrogate endpoints as markers of clinical outcome, (2) utilization of aggressive combination therapies for all stages of HIV infection, including treatment of primary HIV infection (acute seroconversion), (3) elimination of HIV transmission from mother to fetus, (4) continued progress in the management and prevention of OIs, (5) HIV-associated malignancies, (6) HIV-associated neurologic complications, (7) immunologic interventions, (8) management of wasting syndrome, and (9) elaboration of the natural history components of therapeutic studies (e.g., mucosal shedding of HIV, the contribution of OIs to HIV progression, and long-term followup of unique cohorts of HIV-infected individuals who have participated in therapeutic studies). Furthermore, the feasibility of the interdigitating assessment of behavioral and medical endpoints should be evaluated.*

Current Status

NIH supports a broad range of basic, applied, and clinical research activities contributing to a more comprehensive understanding of the natural history of HIV-associated OIs, including their sources, route of transmission, and host risk factors. This information is critical to the development of strategies to prevent opportunistic infectious diseases, including strategies to prevent exogenous exposure.

Elucidation of the complex interactions between the immune system of the HIV-infected host and multiple pathogens is an area of intense interest at this time. The impact of active OIs and their treatment on the immune system, as measured by immune activation, HIV viral load, and HIV viral replication, is currently being assessed in a number of applied and clinical research projects supported by the NIAID. For example, the ACTG has established an ongoing HIV/OI working group to evaluate both the impact of HIV on opportunistic diseases and that of opportunistic diseases on HIV infection. NIAID will continue to encourage and support investigation in this critical area.

NCI places a high priority in its clinical trials program on AIDS-associated malignancies. In addition to hypothesis-driven trials evaluating antitumor, survival, and virologic and immunologic

endpoints, other issues of interest include drug–drug interactions and tumor-specific symptom relief.

Changes in cervical-vaginal shedding of HIV over the course of the menstrual cycle are currently being evaluated in an NICHD/NIAID-funded study performed through the WIHS, and evaluation of cervical-vaginal viral shedding and perinatal transmission is being evaluated in the context of the NIAID/NICHD/NIDA-funded WITS.

Many of the crosscutting areas that are specific to pediatric HIV infection are being addressed in the context of clinical trials being conducted by the NIAID/NICHD-funded PACTG. For example, in the PACTG there are pilot protocols currently being designed to evaluate the impact of aggressive combination therapy in HIV-infected neonates that will assist in addressing the efficacy of additional modalities to reduce perinatal transmission (see NIH response to **Recommendation 62**); studies evaluating immune-based therapies in infected children; and a long-term outcome study (ACTG 219) that follows through age 21 all children (infected and uninfected) whose mothers participated in perinatal studies and all infected children who have participated in any PACTG protocol.

Future Actions

NIH concurs with this recommendation and will continue to support the aforementioned priorities in its clinical trials programs. NIH also will continue to interdigitate, where appropriate, behavioral and medical endpoints in the clinical trials that the ICDs support.

Recommendation 323 [Clinical Trials ARP Report, p. 11, No. 10]

Better definitions of AIDS and AIDS-related research must be established so that AIDS funds are appropriately allocated. An improved database at the NIH is critical to both the management of NIH fiscal resources and the tracking of research progress.

Please refer to the NIH response to Recommendation 44.

Ad Hoc Panel on Complementary and Alternative Medicine Therapies Research Recommendations

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Recommendation 324 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 2, No.1]

The OAR should establish an ongoing advisory panel on CAM for HIV disease to help identify and distinguish therapies with apparent promise from those with potential harm. This panel should be comprised of scientists experienced in HIV and/or CAM research and individuals involved in the use of alternative therapies.

Current Status

The NIH AIDS research program benefits from input of scientific and community groups in its scientific planning and research efforts. OAR will look to OAM and its Alternative Medicine Program Advisory Council for information regarding CAM therapies for HIV disease, including assistance in identifying new HIV-related CAM approaches and in providing suggested research criteria by which efficacy and effectiveness should be judged. OAM will assist the OAR in establishing an advisory panel on CAM for HIV disease to identify and distinguish therapies with apparent promise from those with potential harm. In addition, OAM will share its database of individuals interested in or involved with CAM treatment and research in AIDS.

Recommendation 325 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 2, No. 2]

The OAR, in collaboration with its HIV-CAM Advisory Panel, should work in partnership with the NIH Office of Alternative Medicine (OAM) to establish an operational definition of complementary and alternative therapies for HIV disease and to construct a taxonomy to categorize therapies in this area.

Current Status

OAM has already established a working definition of CAM for all areas of CAM to include HIV disease. Construction of a taxonomy to categorize therapies in this area is a forthcoming activity that OAM plans to achieve with OAR involvement. OAR will confer with OAM in the utilization of OAM's working definition of CAM and its catalog of CAM-related information on HIV therapies supported by NIH.

Recommendation 326 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 3, No. 3]

Once a definition of complementary and alternative therapies is developed, the OAR should sponsor a survey on the current use of these therapies by persons living with HIV. This survey should include participants in NIH-sponsored clinical trials and natural history cohorts.

Recommendation 327 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 3]

An operational definition of CAM as it relates to HIV disease, collaboratively derived by the OAR, the OAM, and appropriate representatives from the HIV-affected and CAM scientific community, and used throughout the NIH in budgetary and research planning of its AIDS program.

Recommendation 328 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 3]

The Panel believes that successful consideration of HIV-related CAM approaches will be successful if there is identification and prioritization of HIV-CAM research approaches for agents that:

- *Are in widespread use or potentially may come into widespread use (in the United States and abroad)*
- *Can be accessed easily and used by underserved populations*
- *Have large potential impact on the HIV-infected community*
- *Have extremely low or high potential harm*
- *Show scientific rationale*
- *Are potentially cost-effective or costly*
- *Have potential for self-care*

Current Status

Through its AIDS center at Bastyr University, OAM has already cooperated and collaborated with the NIAID MACS to serve patients who currently are being followed under the MACS program on their use of CAM therapies following diagnosis and possibly treatment for HIV disease. Additional surveys are anticipated and would be planned with OAR support and involvement to further define and delineate CAM usage in HIV-infected individuals.

OAM supports involvement by OAR in the further development of an operational definition of CAM as it is related to HIV disease, as well as involvement in furthering HIV-CAM research approaches for studying HIV-related CAM treatments that are widespread, can be accessed easily (especially by underserved populations), have large potential impact on the HIV-infected community, have extremely high or low potential harm, show scientific rationale, are potentially cost-effective or too costly, and have the potential for use in self-care. OAM further endorses the concept that HIV-CAM research efforts should involve investigators who have sufficient familiarity and experience in conventional research methodology. OAM intends to increase the cadre of such researchers by holding conferences and research meetings targeted toward AIDS-related research issues.

Recommendation 329 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 3]

The field of HIV-CAM research will benefit as a whole if alternative medicine investigators acquire greater familiarity with and experience in conventional medical research methodology.

Recommendation 330 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 3, No. 4]

The OAR and the HIV-CAM Advisory Panel should work in partnership with the OAM to sponsor workshops on the research methods appropriate for the evaluation of CAM therapies for HIV disease. The utility of available methods and their limitations should be reviewed, and approaches to strengthen their scientific basis should be identified. Participants in these workshops should include representatives from OAR, OAM, the ICDs, the Food and Drug Administration (FDA), and CAM practitioners and researchers as well as HIV-infected persons who use CAM therapies.

Recommendation 331 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 4, No. 5]

The OAR should help facilitate linkages between persons interested in the evaluation of CAM therapies for HIV disease and investigators with experience in designing clinical trials or laboratory investigations.

Current Status

OAM fully supports working with OAR in hosting workshops on research methodologies appropriate for the evaluation of CAM therapies for HIV disease. OAM believes that limitations of research methodologies, as well as their availability, should be critically evaluated and subjected to the standard rigorous review common to NIH. Participation from OAR, OAM, other interested or involved ICDs, FDA, CAM practitioners, and particular CAM researchers is anticipated.

OAM is particularly interested in forming liaisons between persons interested in the evaluation of CAM therapies or HIV disease and experienced investigators who can assist in the design of clinical trials and/or laboratory investigations of candidate therapies and interventions.

Recognizing the mission of OAM, OAR is offering its assistance to the OAM leadership in sponsoring a research methodology meeting on HIV and CAM approaches. OAR has conveyed its interest in assisting OAM in the planning and implementation of such a meeting, offering the involvement of OAR senior staff members, planning expertise, and resources. OAR looks forward to working with OAM in this effort.

Recommendation 332 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 4, No. 6]

The OAR should, where appropriate, work with and provide supplemental funding to support OAM research activities and program goals in the area of HIV disease.

Current Status

OAM anticipates OAR support where appropriate in providing supplemental funding to support CAM-related research in clinical trials on HIV disease. OAM believes that the funding mechanisms should be further defined prior to solicitations being announced to the research communities.

Recommendation 333 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 4, No. 7]

> *The OAR should work with the OAM to sponsor workshops to educate individuals interested in the evaluation of candidate CAM therapies for HIV disease about the preparation of NIH grant applications and the processes by which such applications are evaluated.*

Current Status

Workshops have been planned and have been used by OAM to educate different segments of the community relative to CAM areas. OAM, therefore, anticipates OAR assistance in sponsoring workshops related to CAM.

Recommendation 334 [*Ad Hoc* Panel on CAM Therapies Research Report, p. 5, No. 8]

> *The OAR should work with the OAM and the DRG to suggest individuals who may serve as* ad hoc *members of study sections that are considering applications concerning CAM therapies for HIV disease. Criteria for the selection of* ad hoc *study section members should include those currently used by DRG as well as experience in the scientific evaluation of novel therapeutic approaches and a familiarity with the concepts and practices of CAM therapies.*

Current Status

OAM will work with OAR by sharing information regarding individuals who are qualified to and interested in the review of applications relative to CAM. This information will be shared simultaneously with DRG. Since OAR does not designate members of IRG, OAR will work with OAM in suggesting qualified people to serve on AIDS-related IRGs.

***Ad Hoc* Panel on Opportunistic Infections Research Subgroups Recommendations**

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Recommendation 335 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 2, No. 1a]

Reinvigorate the basic science research effort on AIDS-associated OIs.

The highest priority of the NIH effort in OI research should be basic scientific studies of organism life cycles, metabolism, transmission, epidemiology, pathogenesis, and host response.

Current Status

NIH recognizes the need for a renewed emphasis on basic research on the pathogenesis of AIDS-associated OIs. NIAID is responsible for the majority of NIH-supported basic microbiological research on OIs through the extensive grant portfolios of both the DMID and DAIDS. Using this investigator-initiated research as a base, NIAID supports a large number of applied studies for the development of better diagnostics, drugs, and vaccines for OIs. In addition, NIAID currently uses contract resources for the evaluation of novel experimental therapies in animal models of OIs.

NHLBI supports a substantial number of basic research grants aimed at understanding host microbial interactions in the lung at the cellular and molecular level. The majority of these grants address the pathogenesis of TB and *Pneumocystis carinii* pneumonia (PCP). Most of the current portfolio resulted from highly focused Institute initiatives (RFAs), but the number of investigator-initiated grants is growing.

Future Actions

NIAID will continue to support and stimulate basic and applied research through PAs, the NCDDG-OI, and the Molecular Approaches to Targeted Antiviral Research Group Programs, as well as animal model drug evaluation programs. In addition, the AIDS Research and Reference Reagent Program will be increasingly utilized to support production and distribution of reference reagents vital to the pace of basic and applied research. NIH will closely monitor, encourage, and give high priority to hypothesis-driven investigations on the pathogenesis of AIDS-associated OIs, emphasizing the application of state-of-the-art methods to *in vivo* studies.

Recommendation 336 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 2]

The NIH should stimulate progress in these areas by support of investigator-initiated grants that encourage collaboration between basic research scientists and between basic research scientists and clinical investigators

The NIH should structure funding mechanisms in such a way as to diminish the complexity of the grant application process (e.g., requirements that collaborators be at different institutions or that industrial collaborations be established) and maximize the process of scientific discovery.

Current Status

NIH will continue to use and seek additional funding mechanisms to entice established laboratories in related fields to enter AIDS research. Many of the grant-supported investigators who study organisms considered to be OIs in the context of HIV infection are encouraged to collaborate with other established AIDS researchers and be supported with AIDS funds.

NIAID funds National Research Service Award applications (F32s) from postdoctoral fellows on the basis of scientific merit and training potential, regardless of the main research emphasis of their mentors. Through this mechanism, fellows from non-AIDS laboratories have received funds for HIV/AIDS-related projects. In recent PAs, such as PA 96-068 "Innovative Drug Discovery Research in AIDS OIs," NIAID has included R29s (FIRSTs), R03s (small grants), and competitive supplements to existing NIH grants as mechanisms by which investigators in related fields could obtain funds for preliminary studies related to HIV/AIDS. In addition, NIAID recently has released PA 96-069 "Collaboration for Advanced Strategies in AIDS OIs" to specifically encourage translation-research collaborations between laboratory and clinical researchers. The previously mentioned R03s (small grants) and competitive supplements to ongoing NIH-funded grants in response to a PA are mechanisms supported by NIAID that allow accumulation of preliminary data that would allow the submission of a competitive R01. Finally, developmental projects sponsored by CFARs are an additional mechanism for funding small pilot projects.

NCI has added additional support to its Comprehensive Cancer Centers for studies on AIDS-associated malignancies and funded new grants through RFAs specifically targeted to basic research on the etiology and biology of AIDS-related neoplasms.

NHLBI RFA programs have fostered new ties between basic biomedical scientists, as well as engendered collaborations between basic and clinical investigators.

Future Actions

NIH will continue to support the funding mechanisms highlighted above and expand support for those mechanisms, such as R03s and competitive supplements, that have been successful in attracting new investigators from related fields into HIV/AIDS research. NIAID will implement several strategies to enhance the funding of "high-risk/high-payoff potential" pilot research. The PA mechanism is being expanded and strengthened with the addition of set-aside funds and the encouragement of small R03 applications. These awards are for shorter duration and fewer funds than traditional R01 grants. Applications can be reviewed on an accelerated schedule, which should encourage the expeditious undertaking of pilot studies that can be the basis of larger R01s if the preliminary results are promising. In addition, NIH is experimenting with a scoring system for traditional R01s that would include separate scores for novelty and potential impact. This scoring system will allow the ICDs to assign differential weights to the separate components of the new priority score and make funding decisions accordingly.

NIH agrees with the Panel that the complexity of the grant application process should be minimized. Under the present NIAID reinvention efforts, restrictions on collaborations (such as

those that require collaborators to be at different institutions or that require industrial collaborations be established) will no longer be a part of PAs.

NHLBI has streamlined the grant application process for RFAs and other initiatives, e.g., by using modular budgets and "just-in-time" submission of budgetary and "other support" information.

NIH also will strive with DRG to redesign the whole process of multidisciplinary grant review. Multidisciplinary approaches to scientific problems represent an emerging need, and their potential importance extends to all areas of biomedical research, not just AIDS research. Thus, one of the challenges is to start structuring the appropriate review process to foster these efforts more effectively.

Recommendation 337 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 2]

The NIH should encourage research into the pathogenesis of opportunistic diseases in their natural hosts and in relevant animal model systems.

Please refer to the NIH response to Recommendation 335.

Recommendation 338 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 2]

A program of small pilot grants should be implemented to support preliminary projects of high risk but significant potential promise. The intent of these grants (e.g., approximately $50,000 per year for 1 to 2 years) would be to test a principle or gather sufficient preliminary data for submission of an R01 grant application.

Please refer to the NIH response to Recommendation 336.

Recommendation 339 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 2, No. 1B]

The NIH currently supports an active program of research in this area, and it is expected that the productivity of this effort will be enhanced significantly by the recommendations discussed elsewhere in this report, including those that call for the following:

increased support for investigator-initiated research.

Please refer to the NIH response to Recommendation 1.

Recommendation 340 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 2, No. 1B]

expert peer review informed of the scientific priorities of the annual NIH Plan for HIV-Related Research.

Please refer to the NIH response to Recommendation 6.

Recommendation 341 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 2, No. 1B]

increased efforts to encourage young investigators to enter AIDS research.

Please refer to the NIH response to Recommendation 11.

Recommendation 342 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 2, No. 1B]

increased efforts to attract established investigators with expertise in related areas to pursue AIDS-related research.

Please refer to the NIH response to Recommendation 12.

Recommendation 343 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 3, No 1C]

To further progress in this area, the Office of AIDS Research (OAR) and relevant Institutes, Centers, and Divisions (ICDs) should increase and better coordinate their efforts to foster research on AIDS-related OIs and continue to solicit the advice of non-Government scientists in identifying new research needs and opportunities in this area. As many of the AIDS-associated OIs also cause disease in individuals with other types of immunodeficiency and research on these pathogens is consequently supported with both AIDS and non-AIDS funds, it will be important to view the NIH portfolio in this area as defined by scientific issue rather than funding mechanism.

The OAR should establish an external expert advisory group to advise the OAR concerning evolving opportunities and needs in AIDS OI research. This group should review the NIH OI research portfolio on a yearly basis and recommend adjustments for programs that need to be updated or changed. This group should encourage improved reportability and accountability of programs sponsored by various ICDs. A consistent standard for high-quality science should be emphasized, and indicated resources should be redirected away from less productive programs. Many AIDS-associated OIs also cause disease in persons with other types of immunodeficiency, and research on these infections is supported with both AIDS-designated and non-AIDS funds; thus, the advisory group should monitor the NIH's OI research portfolio as a whole rather than only that portion supported by AIDS-designated resources. This approach will ensure better overall assessment and coordination of NIH's OI research activities.

Current Status

NIH recognizes the need for improved coordination of research on AIDS-associated OIs and already utilizes various nongovernmental groups to provide advice and guidance in this research area. At this time, NIH does not perceive the need to establish a formal advisory group for this purpose.

NIH supports a comprehensive, multifaceted research program for the prevention and management of OIs that encompasses basic, applied, and clinical research on multiple pathogens. Although primary responsibility for facilitating research of most HIV-associated infections rests within NIAID, other ICDs and other Government agencies also play critical roles in furthering progress in all facets of this research.

NIAID has routinely involved non-Government scientists and community representatives in the review and planning of Institute research efforts. In addition to NIAID's Advisory Council, its Microbiology and Infectious Diseases subcommittee and ARAC provide forums for the non-Government scientific community to help develop NIAID's research initiatives. Since 1990, NIAID has invited panels of outside experts, both in AIDS and non-AIDS research, and community members to assess the success of the major programs and to recommend future scientific directions. The programs assessed have included OI clinical programs and specific OI initiatives such as the NCDDG-OI.

Coordination to share information, provide effective maximum coverage in critical research areas, and avoid duplication is a necessity. NIAID's divisions have established effective means for collaborating with each other in the planning and implementation of an OI research agenda. Some examples include the monthly meetings to share information and coordinate program initiatives for OIs (DAIDS, DMID, Division of Intramural Research [DIR], DAIT, and the FDA); the NIAID Tuberculosis Working Group, which coordinates all NIAID-sponsored TB activities; and DAIDS/DMID collaborations in clinical trials, such as the Mycoses Study Group and the Collaborative Antiviral Study Group. There also are inter-Institute collaborations, such as the NIAID and NHLBI participation on the Department-wide TB Task Force.

Extra-Institute examples of coordination and collaboration include a collaboration with WRAIR for PCP drug development; a CDC and Pan American Health Organization (PAHO) collaboration with the NIAID-sponsored TB prophylaxis clinical trial; NIAID representation on the WHO Immunology of Mycobacteria Steering Committee and its Vaccine Development Working Group; membership in the Working Group on Waterborne Cryptosporidiosis, which also includes participation from the Environmental Protection Agency (EPA), CDC, FDA, and State and local health authorities; and a collaboration with the French L'Institut National de la Sante et la Recherche Medicale (INSERM) for TB clinical trials.

NHLBI regularly solicits advice from nongovernmental scientists through the use of RFA meetings and Special Emphasis Panels in areas relating to TB and AIDS research. NHLBI holds yearly meetings of the TB Academic Awardees in conjunction with the Annual National Coalition to Eliminate Tuberculosis Meeting. CDC representatives attend both meetings.

NCI established an AIDS Malignancy Working Group, a group of non-Government scientists and oncologists, to provide advice on the etiology, biology, immunopathogenesis, epidemiology, diagnosis, and treatment of AIDS-associated malignancies.

Future Actions

An OAR-sponsored workshop will assist in the articulation of research priorities that will be integrated into the annual NIH Plan for HIV-Related Research. OAR, in collaboration with the appropriate ICDs, will convene this workshop in 1998.

OAR will participate in the meetings organized by NIAID to share information and coordinate program initiatives for AIDS-associated OIs. In addition, negotiations with NIAID are ongoing concerning the optimum way to share information about AIDS and non-AIDS-associated OIs in order to obtain a comprehensive view of the NIH portfolio in this area.

OAR will take the lead role in further improving communication between ICD program staff and investigators involved in OI research by creating a central OI Web page. Communication between ICD program directors will be improved through the development of such a central OI information resource and through the expansion of the NIAID OI Working Group to include participation by NIAID program directors, intramural investigators from the Clinical Center, microbiologists from the FDA, and other ICD program directors. This group will exchange information and advise each other on the highest quality state-of-the-art science.

Through the established NIAID Advisory Council, ARAC, and nongovernmental panel evaluations of specific disease portfolios, overall assessment and coordination of OI research activities will be maintained.

Recommendation 344 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 3]

Existing NIH databases of funded research activities are inadequate for assessment of funds supporting OI research. The NIH should improve the data management and retrieval systems for ongoing research. The NIH data bases should be structured to permit greater ease of accessibility and be updated on a regular basis.

Please refer to the NIH response to Recommendation 43.

Recommendation 345 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 3]

The OAR, in collaboration with the relevant ICDs and industry representatives, should establish a regular review of OI research by sponsoring focus meetings on individual pathogens and on groups of related pathogens. This process should result in the development of goals that are jointly recognized by academic, Government, and industry

scientists and will facilitate greater communication of relevant results and more rapid exploitation of research opportunities.

Current Status

NIH supports most of the basic biomedical research on OI pathogens. These studies provide critical information to be applied to the diagnosis, treatment, and prevention of associated diseases. However, more progress is needed in understanding the fundamental biology and pathogenesis of AIDS-associated OIs.

OAR is acutely aware of the need to stimulate further research to understand the fundamental biology and pathogenesis of AIDS-related OIs. To best accomplish this objective, OAR has incorporated the scientific goals expressed in the context of this recommendation in the NIH Plan for HIV-Related Research. In this Plan, the elucidation of the pathogenic mechanisms of HIV-related OIs has been identified as one of the most pressing scientific issues to be pursued.

Future Actions

OAR will convene a workshop on OIs that will include participation of representatives from academia, industry, the community, and the Federal Government in 1998. The goal of this workshop is to identify critical gaps in the knowledge of OIs that need to be addressed and to establish scientific priorities. These priorities will in turn become an integral part of the NIH Plan for HIV-Related Research. The workshop participants also will determine the frequency of future workshops as there will likely be a need to convene additional workshops to maintain focus and to address in a timely manner the evolving needs and scientific opportunities in OIs research.

Recommendation 346 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 3, No. 1D]

The NIH should take a more productive approach to training of scientists for the study of OIs. At present, the Subpanel believes the following:

There is at present a crisis in the relative lack of incentives to enter the field of OI research and inadequate opportunities and support to train young investigators in OI research.

Current Status

NIH utilizes innovative funding mechanisms to provide short-term funding for new investigators to develop research programs. NIAID, the principal ICD supporting OI research, presently funds R29s at a higher percentile compared with R01s. The CFARs support OI research with developmental funds. In addition, NIAID has included R29s, R03s (small grants), and competitive supplements to ongoing funded NIH grants in recent PAs to allow funding of preliminary studies.

Future Actions

NIH will continue to support new investigators in OI research through the above funding mechanisms and identify additional opportunities to do so.

In addition, please refer to the NIH responses to Recommendations 11–13.

Recommendation 347 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 3]

The NIH should undertake to make it easier for young investigators to obtain initial NIH research support. Possible approaches might include a separate review process for R29 grants or more generous funding levels for these applications. Establishment of a program of short-term (1 to 2 years) grants to provide initial support to promising young scientists should also be considered.

Please refer to the NIH responses to Recommendations 11 and 346.

Recommendation 348 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 3]

The NIH should continue to enhance training programs that encourage young scientists to pursue research on OIs. In addition, funding support should be considered for established investigators in one field to retrain in a laboratory studying opportunistic pathogens, and for young investigators within mentorship programs.

Please refer to the NIH responses to Recommendations 11–13 and 346.

Recommendation 349 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 4]

The NIH should sponsor short courses (3 to 4 weeks) on opportunistic pathogens to attract young investigators as well as established investigators working in related fields to pursue research on AIDS-associated OIs.

Current Status

NIH agrees that short courses on basic research related to various AIDS-associated OIs should represent a viable way to attract new and established investigators to the field. This objective could be accomplished by academic centers, which may apply for support through the R13 mechanism.

Future Actions

Discussions concerning courses on OIs will be addressed at the upcoming OAR-sponsored workshops on AIDS-associated OIs.

Recommendation 350 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 4, No. 2]

The NIH should pursue innovative approaches to foster the transfer of new laboratory findings to early "proof of principle" clinical evaluation

The OI Subpanel suggests the following strategies to accomplish this goal:

The OAR should facilitate the translation of promising basic research findings to clinical applications. A translational research coordinator within the OAR, and informed by the external advisory panel on OIs described above, should work with basic scientists and industry to identify promising opportunities in their areas and help establish productive collaborative efforts.

Current Status

Increasing the number of new and experienced basic and applied scientists, including immunologists, molecular biologists, microbiologists, virologists, and parasitologists, working in the OI field will ultimately be the most effective way to move promising scientific approaches into clinical investigation.

In the interim, NIH has taken several steps to move this field forward. A NIAID PA was issued this year specifically to foster the transfer of new laboratory findings to early "proof of principle" clinical evaluation. This PA has three annual receipt dates. Preliminary evaluation of the utility of this funding mechanism will be possible after the first round of applications is received and reviewed.

NIAID has also had recent successes in providing cross fertilization between disparate research groups in the interests of fostering translational research. For example, ACTG OI leadership has attended the annual NCDDG-OI meeting in order to both become familiar with early research developments and express clinical needs to the basic research community. By the same token, basic scientists have been invited to participate in ACTG meetings to become more familiar with the clinical needs and research issues faced by the clinical research community. NIAID has also helped ease the translation of basic research to the clinic through regulatory (IND) support of investigators.

While taking these steps, NIAID has issued numerous RFAs and RFPs to maintain an active portfolio of resources available to scientists including *in vitro* biochemical and microbiological screens, *in vivo* animal model systems, and various OI research reagents. These resources are limited, however, and NIAID supports the recommendation that resources available through NCI be made available for the identification and production of candidate agents for OIs in which the pharmaceutical industry has little interest.

Future Actions

NIH will continue to use a number of mechanisms to translate promising basic OI-related research findings to clinical applications. These efforts will be supported through OAR and ICD initiatives that focus on developing effective collaborations and providing opportunities for exchange of information, timely assistance, and direction. At the current time, there is not sufficient justification to establish a translational research coordinator within OAR who would receive guidance from an external advisory group on OIs.

Recommendation 351 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 4]

> *The OAR should work with the ICDs and the Small Business Administration to improve the quality and impact of AIDS-related research funded by the NIH through the Small Business Innovative Research (SBIR) grant program. These funds should be focused on important unmet needs in AIDS research through a new program of Request for Applications (RFAs) issued to small biotech or pharmaceutical firms. The topics of these RFAs should be defined by OAR and ICD staff members, in consultation with Government and non-Government scientists, to target emerging opportunities for the development of diagnostics and therapeutics for HIV infection and its associated complications.*

Current Status

NIH has piloted several projects intended to improve the scientific focus and quality of research funded through the SBIR program. In addition, many program staff work closely with SBIR applicants to improve the relevance of their proposals.

As part of a reinvention effort, NIAID and nine other ICDs are piloting a “fast-track” approach where Phase I and Phase II applications are evaluated concurrently. The intent is to accelerate the awarding of Phase II funds to successful, high-quality SBIR projects.

NIAID also organized the first regional workshop for SBIR/STTR applicants, which was held last fall in New England. This workshop focused on advice for preparing applications and selecting the right funding mechanisms. A booklet of advice on writing SBIR and STTR proposals is available from NIAID and through the NIH home page on the Internet.

NIH continues to promote projects intended to improve the scientific focus and quality of research funded through the SBIR program. In addition, program directors work closely with SBIR applicants to improve the relevance of their proposals.

Future Actions

Additional workshops are planned for other parts of the country.

In addition, please refer to the NIH response to Recommendation 31.

Recommendation 352 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 4]

The NIH should strengthen the study sections that review SBIR grants related to AIDS with respect to scientific expertise and familiarity with contemporary scientific needs and opportunities, as articulated in the annual NIH Plan for HIV-Related Research.

Please refer to the NIH response to Recommendation 7.

Recommendation 353 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 4]

The Area Review Panel evaluating the Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI) should consider the potential contribution of the program to identify and produce candidate agents for the treatment of OIs for which there is little or no interest within the pharmaceutical industry. Should the AIDS-related activities of the DTP program be continued in the future, they may provide a vehicle to advance candidate drugs from the research laboratory to a stage where an Investigational New Drug (IND) application can be filed with the Food and Drug Administration (FDA), permitting initial clinical evaluation. Should promising agents be identified in "proof of concept" clinical trials, it is likely that the interest of the pharmaceutical companies in further developing such agents may be increased substantially.

Current Status

In response to the Drug Discovery Area Review Panel's recommendation, the NCI Office of Technology Development published a public notice in the August 1996 *Federal Register* announcing NCI's intention to form a CRADA with responsible investigators and commercial firms to screen its collection of open compounds and natural product extracts for novel agents directed against antibiotic-resistant microorganisms and infections of an emerging, opportunistic nature. This issue is also addressed in the NCI response to **Recommendation 300**.

Future Actions

NCI enthusiastically welcomes this opportunity to contribute toward research on anti-OI agents and will support this effort to its fullest extent.

I. PNEUMOCYSTIS CARINII

Recommendation 354 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 8]

Basic studies elucidating the beneficial or deleterious roles of the host immune responses directed against PCP, the effects of the organism on lung physiology, and basic research for antigenic and serologic reagents are recommended. The development of immunotherapies and vaccines should proceed more rapidly based on the results of these studies. Research leading to a clearer understanding of the establishment of infection (e.g., the role of organism attachment to host cells) is recommended.

Recommendation 355 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 8]

The pathology that PC exerts on the host remains poorly understood, yet the development of effective prophylaxis or therapeutic measures will likely be greatly expedited by understanding better the response of both the immune-competent and immunosuppressed hosts to the organism.

Recommendation 356 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 8]

The Subpanel recommends that research leading to a clearer understanding of the establishment of infection (e.g., the role of organism attachment to host cells) be emphasized.

Recommendation 357 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 8]

The Subpanel recommends supporting research to develop a noninvasive diagnostic test that would discriminate between acute-phase infection, remote infection, or exposure.

Recommendation 358 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 9]

Development is needed of a rapid noninvasive diagnostic test that would discriminate between acute-phase infection and remote infection or exposure.

Recommendation 359 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 9]

The Subpanel recommends support for the development of therapeutic and prophylactic modalities. A goal should include an identification of a battery of agents, including combinations of chemotherapeutic and immunotherapeutic agents, to prevent the emergence of drug-resistant organisms.

Recommendation 360 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 10]

Research is needed to develop strategies to detect drug resistance and identify mechanisms of resistance used by the organism.

Recommendation 361 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 10]

It is critical to revise current mechanisms for introducing candidate compounds identified through drug-screening programs into safety and tolerance trials followed by efficacy evaluation. Suggestions include an OAR-affiliated translational research

coordinator working with expert external advisors to select promising drugs from basic OI research for clinical development and to oversee the early transition of those candidate agents into efficacy evaluations.

II. FUNGAL INFECTIONS

Recommendation 362 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 11]

Serial studies of the incidence, prevalence, and clinical course of at-risk patients of different age groups for a variety of fungi such as Candida, Pneumocystis, Cryptococcus, Aspergillus, Histoplasma, Coccidoides, *etc., are necessary.*

Recommendation 363 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 12]

Investigations of the basic molecular pathobiology of fungi should be encouraged and supported. It will be important to attract molecular biologists currently conducting research in other eukaryotic systems to interact with mycologists who understand clinical disease.

Recommendation 364 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 12]

The NIH should encourage development of reliable methods for the rapid diagnosis of infection using nucleic acid or protein-based detection strategies and should coordinate this work with industry.

Recommendation 365 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 13]

The NIH should support basic science initiatives to identify drug targets, drug-resistance mechanisms, animal models, clinical strategies of treatment and prophylaxis, and immune modulation.

III. VIRAL INFECTIONS

Recommendation 366 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 15, No. 1]

CMV, HSV, VZV: Identify and understand mechanisms of viral latency, including the viral and host functions that restrict viral productive replication. Investigate viral genes controlling dissemination, tissue invasion and disease following reactivation, and the relationship of disease to immunodeficiency. Investigate host cell functions that restrict intracellular viral replication. Understanding these functions will provide additional targets for antiviral therapy and vaccine development. Investigate mechanisms of drug resistance and the impact of drug resistance mutations on pathogenesis in animal models and in patients.

Recommendation 367 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 15, No. 2]

KSHV: Identify viral genetic determinants causing cell proliferation and their effect on the host cell. Determine the cellular and molecular events that lead to proliferation and the cell types involved.

Recommendation 368 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 16, No. 3]

EBV: Understand the mechanisms of EBV-induced lymphocyte proliferation. Studies should be aimed at the function of latent gene products and their interaction with cellular signaling pathways as well as on ways to use this information to control proliferation and understand the particular determinants associated with lymphoproliferative disease.

Recommendation 369 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 16, No. 4]

Other viruses: Investigation of the viral and host genetic basis of how viral persistence, immune response, or the damage to specific tissues leads to disease.

Recommendation 370 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 16, No. 1]

Understanding mechanisms of immune control

a. productively infected cells: CMV, HSV, VZV, HHV-6, HHV-7, JCV, hepatitis viruses

b. latently infected cells: CMV, KSHV, EBV, HPV, HSV, VZV, HHV-6, HHV-7, JCV, hepatitis viruses

c. proliferating cells: KSHV, EBV, HPV

Recommendation 371 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 16, No. 2]

Identification of viral antigen targets of immune control. Determine the spectrum of antigens that are required for the induction of protective viral immunity.

Recommendation 372 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 16, No. 3]

Understanding the contribution of the host immune response to disease (immunopathology).

Recommendation 373 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 16]

More work on the patterns of viral gene expression or antibodies needs to be completed in order to have diagnostic tests that are predictive of disease and that can be used to make informed choices in therapy. Diagnostic tests need to be developed that can be applied to readily accessible cells or fluids. Development of rapid standardized methods to identify infections with drug-resistant viruses is needed.

IV. MYCOBACTERIAL OIs

Mycobacterium tuberculosis

Recommendation 374 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 21]

TB research must be accorded the highest priority by the NIH. TB is not simply a U.S. problem or an HIV-related problem. TB cannot be controlled in this country until it is controlled worldwide. The current level of NIH funding of TB research is appropriate given the public health importance, clinical needs, and the scientific opportunities.

Recommendation 375 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 21]

To optimize research efforts on TB, increased coordination is required at multiple levels: within the PHS (NIH and CDC), among the NIH Institutes, and within NIAID (DMID, DAIDS) as well as with other funding agencies (WHO). This coordination must be sustained and enhanced, independent of the current high level of public and political interest.

Recommendation 376 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 21]

The NIH should give special consideration to ensuring that successful research projects and programs are sustained. The flurry of RFAs and RFPs has galvanized the scientific community. This impressive effort will, however, stall unless special consideration commensurate with the importance of this topic is accorded to the review process for competitive renewals.

Recommendation 377 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 21]

Scientific areas of particular importance include studies of fundamental mechanisms of drug resistance and drug action, new drug targets, latency, and protective immunity. The NIH should give a high priority to basic and applied research on TB vaccine development.

Recommendation 378 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 21]

To increase our understanding of TB and develop new drugs, a comprehensive effort is essential to address and resolve the disincentives to pharmaceutical companies, given the low incidence of TB in the United States.

Recommendation 379 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 21]

The NIH should redirect major clinical trials efforts to international sites in areas of high incidence of TB (and HIV).

Mycobacterium avium

Recommendation 380 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 23]

The NIH should convene a consensus panel to review current research activities and scientific opportunities concerning MAC. The NIH should develop an expanded scientific agenda through RFAs and Program Announcements.

Recommendation 381 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 23]

The NIH should encourage research in the areas of protective immunity, pathogenesis, mechanisms of drug resistance, and identification of new drug targets.

Recommendation 382 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 23]

The NIH should address the issue of protective immunity in humans through epidemiologic studies in areas of high and low prevalence of disseminated MAC in AIDS patients.

V. TOXOPLASMA GONDII

Recommendation 383 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 24]

There is little understanding of the role that parasite-versus-host genotypes play in disease, and it remains unclear why toxoplasmosis develops in only a subset of patients. Further research is needed to define the relationship of both the parasite and host genotypes to disease pathogenesis and clinical outcomes.

Recommendation 384 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 24]

Research is needed to carefully define the contribution clonal type may play in determining differences with respect to drug sensitivity, virulence, and immune response.

Recommendation 385 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 24]

There is an urgent need to define fundamental metabolic pathways of the parasite, especially bradyzoites. Little is known about the basic metabolism of tachyzoites, and even less is known about the metabolic processes of bradyzoites. Intermediary metabolism studies are needed to define what pathways are present and how they differ from the mammalian host. Research in this area is needed and represents the best hope of ultimately identifying new targets and new therapies. As such, it deserves high priority.

Recommendation 386 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 25]

The host-parasite interaction is a critical area for future investigation.

a. *Research on the parasite cytoskeleton and on the mechanism of motility is warranted, given the involvement of the parasite cytoskeleton in host cell invasion.*

b. *Characterizing the process of parasite secretion and defining the biological function of secreted proteins are essential for understanding the mechanism of intracellular infection. These studies will likely define new targets for therapeutic intervention.*

c. *Research is necessary to increase understanding of the role that specific* T. gondii *genes play in virulence. Knowledge of these genes should provide the foundation necessary to develop new therapies and/or vaccines.*

d. *Research is needed to identify and characterize genes involved in stage conversion from tachyzoite to bradyzoite or that are necessary for intracellular replication. The identification of essential gene functions will help define novel therapeutic targets.*

e. *Although host genetic factors in murine and human systems are partially identified, there is a need to determine how chronic infection is established and how it may be modulated by the host immune system. The area that is the least clear, and one for which continued attention is needed, is definition of the combination of factors (parasite strain, host genetic background, immunologic components) that are involved in the reactivation of disease.*

Recommendation 387 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 25]

Further development of stable episomal vectors, or those with inducible promoters, and of new strategies to disrupt essential genes or otherwise genetically manipulate these parasites is needed in order to better understand their biology. Research efforts should be devoted to developing those tools. Construction of new libraries should also be supported to further define the genetic constituents of these pathogens and the genes they express at different stages of their life-cycles. The continued lack of an axenic culture system confounds mutant generation and recovery, and the NIH should support efforts to identify axenic culture conditions.

Recommendation 388 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 25]

Improved diagnostic tools are needed, but it is likely that there will be no simple solutions to the problem of distinguishing active from chronic infection. It is not obvious that PCR-based assays are the answer, and new approaches in this area are needed.

Recommendation 389 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 26]

Newly available monoclonal antibodies to parasite antigens as well as cloned genes expressed as recombinant full-length and/or fusion proteins could be used to develop assays and reagents for detection of specific parasite antigens in infected individuals.

Recommendation 390 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 26]

High-throughput screens for microbicidal drugs should be applied to both tachyzoites and bradyzoites, using new systems developed for in vitro *bradyzoite generation and for automated monitoring of parasite growth. These screens are probably best done by the pharmaceutical industry, with input from scientists in academia, although this may not be realistic without more active encouragement of industry involvement. Since eradication of bradyzoites within tissues would eliminate the risk of recurrence from recrudescent disease, identification of drugs with this spectrum of activity is a particularly attractive goal. The development of conditions for* in vitro *differentiation of tachyzoites from bradyzoites, of stage-specific reagents, of transgenic parasites stably expressing enzyme markers (such as β-galactosidase), and of molecular genetic tools is likely to have a major impact on this priority. There also is no substitute for continued screening of promising compounds* in vivo*, since there are discrepancies between the utility of drugs* in vitro *and* in vivo *for* T. gondii*, at least in part due to differences in vitro assay methodology.*

Recommendation 391 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 26]

New drug targets should be identified through the definition of metabolic pathways, targeted sequencing efforts, further definition of the cell biology of invasion and intracellular infection, and new molecular approaches, including mutant generation.

Recommendation 392 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 26]

A human vaccine for T. gondii *is neither practical nor appropriate. Vaccination of meat animals that represent an important source of human infection is, however, a viable approach because (1) such a vaccine can reasonably be tested for efficacy, (2) it would have its own market (*T. gondii *causes spontaneous abortion in sheep), (3) a great deal is known about how to formulate animal vaccines, and (4) such animals are kept under semicontrolled conditions. Although this research would not have immediate benefits, such an approach could ultimately massively reduce the number of chronically infected persons at risk for reactivation.*

Recommendation 393 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 27]

The relative contribution to human infection of oocysts (in cat feces) versus tissue cysts (in undercooked meat) needs clearer definition. This information should be incorporated into proactive public health education programs that transmit the message that toxoplasmosis is a problem and infection with Toxoplasma *is worth avoiding. Wide dissemination of simple recommendations to prevent acquisition of toxoplasmosis could ultimately have a wide impact in lowering the infected population at risk for reactivation.*

VI. CRYPTOSPORIDIUM *AND THE* MICROSPORIDIA *OIs*

Recommendation 394 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 28]

Epidemiologic studies are needed to determine the true incidence of these infections in HIV-infected persons and the threat that they represent to the general population. Basic questions of host range and specificity along with transmission routes need to be determined for the Microsporidia.

Recommendation 395 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 28]

Determine whether isolate/strain variation for Cryptosporidium *exists and if this impacts on pathogenic potential. Develop isolate-specific PCR probes to distinguish isolated strains.*

Recommendation 396 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 29]

Develop and improve both in vitro *and* in vivo *models that can be used to address issues of basic organism biology and pathophysiology, immune responsiveness, prophylaxis and therapy, and differential parasite life cycle stage production. This remains the highest priority of research in this area.*

Recommendation 397 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 29]

Determine molecular and pathophysiologic mechanisms of disease and explore potential treatments directed at amelioration of deranged physiology.

Recommendation 398 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 29]

Gain a more fundamental knowledge of the host-parasite relationship during Cryptosporidium *infection and better characterize immune responsiveness in both immunocompetent and immunocompromised hosts. In addition, determine if latent infections occur.*

Recommendation 399 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 29]

Diagnostic methods are desperately needed for the Microsporidia *and more economical tests are needed for* Cryptosporidium.

Recommendation 400 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 29]

Enhanced detection methods to determine viability of the Cryptosporidium *oocyst in water are needed in order to evaluate new paradigms of water treatment.*

Recommendation 401 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 29]

Identify molecular and biochemical targets for chemotherapeutic and immunotherapeutic approaches to controlling infection.

Recommendation 402 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 29]

> *Give strong consideration to the development of* Cryptosporidium *vaccination strategies that might enhance mucosal responsiveness in humans or control infections in domestic livestock, which could serve as a source of infection to humans.*

Recommendation 403 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 30]

> *Support development of centralized facilities for the production, purification, distribution, and potential cryopreservation of parasites. To some extent, this may impact the desirability for a standardization of* in vitro *and* in vivo *model systems.*

Recommendation 404 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 30]

> *Provide realistic funding support in terms of amount and time to conduct the above research and commit to bring bright, young, energetic investigators into this arena of research.*

Current Status

NIH recognizes that there is an urgent need to strengthen the basic and biomedical understanding of the microorganisms associated with AIDS and the diseases they cause in human beings. NIH will continue to place a high priority on research on AIDS-associated OIs. The FY 1998 NIH Plan for HIV-Related Research was developed taking into account all of the above recommendations. Specific strategies in this Plan are proposed that will permit a better understanding of the OI pathogens and their pathogenic mechanisms as well as the discovery, development, and evaluation of potential regimens of agents for the prophylaxis and treatment of OIs.

NIH currently supports a comprehensive portfolio of research grants, cooperative agreements, and contracts on these microorganisms. Currently supported research is directed toward developing methods to culture and grow these pathogens; developing improved diagnostic assays; charting the incidence, prevalence, and clinical course of these OI pathogens in various populations; developing animal models to study disease pathogenesis; identifying new targets for therapeutics; and facilitating discovery and development of prophylactic and therapeutic agents.

Specific initiatives that target and promote research on OI pathogens are outlined below. NIAID recognizes the importance of supporting and fostering research on OIs. The current research portfolio is divided between studies on fundamental aspects of organism biology and host interactions (supported by DMID) and studies on the critical aspects of targeting drug development and application in HIV-infected hosts (supported by DAIDS). NIAID program staff from different divisions meet regularly in the OI Working Group and work closely together.

NIAID supports investigator-initiated research on OIs in areas of drug discovery, preclinical drug development, epidemiology in HIV-infected populations, host-pathogen interactions, and clinical trials. PA 94-095 “Drug Discovery for Opportunistic Infections Associated with AIDS” encour-

ages applications on *Pneumocystis carinii*, *Cryptococcus neoforms*, CMV, *M. tuberculosis*, *M. avium*, and *Toxoplasma gondii*; and PA 94-019 "Infectious Causes of Diarrhea or Wasting Syndrome in People with AIDS" encourages research on *Cryptosporidium*, Microsporidia, and other infectious causes of AIDS-associated enteric infection. The NCDDG-OI program (e.g., RFA-95-AI-014) supports multidisciplinary, multi-Institute research focused on drug discovery with projects addressing biochemistry, cell biology, immune-based interventions, structural biology and molecular biology.

Pneumocystis carinii (Recommendations 354–361)

The NHLBI AIDS initiatives and grants specifically address research questions in **Recommendations 339-341**. NIAID and NHLBI cofunded the Fourth International Workshop on Opportunistic Protists. NIAID-supported grants and preclinical drug development resources address **Recommendations 342-345** using standardized *in vitro* and *in vivo* systems for propagating *Pneumocystis carinii*. NIAID drug evaluation contracts provide expertise, advice, laboratory training, and critical reagents to the scientific community interested in studying OIs.

Fungal Diseases (Recommendations 362–365)

NIAID recognizes medical mycology as an area in need of development. The NIAID preclinical drug development resources provide research assistance to investigators through generation of preliminary efficacy data using standardized *in vitro* and *in vivo* drug evaluation systems for *Candida*, *Cryptococcus*, and *Histoplasma*. The present research portfolio (medical mycology; DMID) contains approximately 70 awards, including those related to AIDS-associated OIs. Efforts to expand the portfolio are evident in several recent PAs, including PA 96-048 "Expanded Research on Emerging Diseases," PA 96-061 "Modern Vaccines for Mycoses and Measles," and PA (to be numbered) "Aspergillosis, Ehrlichioses, and Drug Resistance." The workshop on "Mycology Research in the 1990's" addressed the increasing importance of medical mycology. Medical mycologists from throughout the United States were invited to discuss research issues and to highlight future research needs.

Five areas were targeted for focus: molecular mycology, diagnosis and treatment, immunology, antigen structure and function, and epidemiology. Each of these five topic areas was targeted for development into a separate workshop/minisymposium cosponsored by NIAID and educational grants raised by the medical mycological community.

Three of the five workshops have taken place: "Molecular Medical Mycology," "Molecular and Immunologic Approaches to the Diagnosis and Treatment of Systemic Mycoses," and "Immunology in Medical Mycology (Part 1 of 2): Antigenic Peptides, Glycobiology and Vaccines." The remaining two workshops in the series are under development and will maintain the established themes.

NHLBI initiatives have encouraged research in this area, and the Institute presently supports several grants relating to fungal infections in the lung.

Viral Infections (Recommendations 366–373)

NIAID funds more than 100 unsolicited investigator-initiated grants on persisting viral infections. The majority of these research projects are concerned with members of the herpesvirus family, all of which have been associated with HIV infection. The emphasis of many of these unsolicited awards is on the interaction between the host and the pathogen. These studies include research on the mechanisms of establishment, maintenance, and release from latency. Also under study are viral interactions with the immune system, including studies to delineate the components of a protective immune response as well as viral strategies to evade the host immune response and viral induction of immunopathogenesis. Research programs on viral mechanisms of replication and pathogenesis may lead to the identification of targets for therapeutic and immunologic interventions.

In addition to the unsolicited investigator-initiated grant portfolio, NIAID supports a number of cooperative agreements and research contracts dedicated to drug discovery and preclinical evaluation of agents against OIs. These cooperative agreements support investigators using molecular and structural strategies to identify viral gene targets for intervention and computer-modeled drug design. Investigators from academic institutions and small pharmaceutical firms provide synthetic compounds and natural products for *in vitro* screening for activity against HSV, CMV, varicella-zoster virus (VZV), and EBV. Agents against HHV-6 also are studied on a nonroutine basis. The use of animal models to evaluate the efficacy of experimental therapeutics against CMV, HSV, and VZV infections has contributed to the introduction of several compounds, such as cidofovir and lobucavir, in clinical studies. Compounds with therapeutic potential for papillomavirus infections are evaluated in animal models using both human and animal papillomaviruses as well as in specialized cell-line or biopsy-culture systems, which allow for the differentiation of keratinocytes and, consequently, the maturation of progeny virions. Clinical trials of therapeutic agents for viruses that cause OIs are carried out by NIAID's Collaborative Antiviral Study Group in immune-competent individuals as well as in patients whose immune systems are compromised by transplantation medications or cancer chemotherapy and in HIV-seropositive patients enrolled in ACTG studies.

NIAID is planning a workshop for fall 1997 to address the state of knowledge of viral mechanisms of viral/immune system interactions that result in immunopathology or viral evasion of immune system control as well as to identify priorities for future research. Viruses to be discussed include those that commonly cause OIs as well as those which do not. These discussions should clarify the similarities and differences between these microorganisms.

NCI maintains a portfolio of research projects on the role of viruses and other factors in the etiology, biology, and pathogenesis of AIDS-related malignancies and research projects on the role and contribution of the immune system in disease pathogenesis and progression. Many of these research projects focus on HHVs and HPVs and their role in a variety of neoplastic sequelae occurring in patients with AIDS. NCI maintains a sizeable portfolio of research projects focusing on animal models of viral-associated and lymphoid malignancies.

The two broad research areas currently under study are (1) the roles of human DNA and RNA viruses and other etiologic factors and/or cofactors, including but not limited to KSHV (HHV-8),

EBV, HPV, CMV, HSV, HIV, and HTLV, in the etiology, biology, and pathogenesis of malignancies associated with AIDS, including but not limited to KS, CNS lymphomas, non-Hodgkin's B-cell and non-B-cell lymphomas, cervical and anogenital carcinomas, body cavity lymphomas, Castleman's disease, leiomyomas and leiomyosarcomas and (2) the characterization of molecular and biological interactions linking long-term carriage of human viruses—including but not limited to KSHV (HHV-8), hepatitis B virus, hepatitis C virus, HHV-6, HPV, HIV, HTLV-1 and -2—with AIDS-associated neoplasms.

In pursuit of these questions, researchers are actively engaged in the following:

- Basic laboratory and animal model studies of pathogenesis and/or neoplasia sequelae and other disease processes associated with the infection and expression of nonhuman retroviruses—such as SIV, simian retrovirus, simian T-lymphotropic virus, bovine immunodeficiency virus (BIV), EIAV, and the murine acquired immunodeficiency syndrome virus—and nonhuman DNA viruses related to human KSHV as models of HIV and AIDS pathogenesis and oncogenesis.

- Investigations to develop appropriate transgenic mouse and SCID mouse models to investigate the pathogenesis and immunopathogenesis of AIDS-associated malignancies.

Mycobacterial Diseases (Recommendations 374–382)

An extensive program of research on TB is supported within NIAID, including over 150 grant-supported projects (R01s, MERIT awards, training awards, and SBIRs/STTRs) and several large contract activities. This research includes investigations into the microbial physiology, molecular biology, and immunology of TB and the host-pathogen interaction, as well as development of improved vaccines, therapeutics, diagnostics, and molecular epidemiological tools.

NHLBI also supports a complementary program including research on the pathogenesis of TB in the lung, behavioral interventions for the treatment of TB, and lung-specific delivery systems for the treatment of TB.

NIH places a high priority on TB vaccine development, as evidenced by the establishment and continued support within NIAID of candidate vaccine screening facilities (in appropriate animal models), as well as support of the basic research that continues to lead to the development of a large number and variety of potential vaccine candidates. NIAID recently (November 7-8, 1996) convened a panel of nongovernmental advisors to review its extramural TB research program; the recommendations of this panel will help guide the setting of priorities and the development of new initiatives for future directions in TB research.

NIAID's TB research efforts are coordinated within the Institute by regular meetings of a TB Working Group. This group has collaborated with other ICDs interested in TB research and the CDC by holding a joint meeting in the spring of 1996 to identify possible areas of future collaborations and to open channels for future communications. NIAID also is represented on DHHS Advisory Council for the Elimination of TB, a CDC-managed task force that advises the Secretary, and the WHO Immunology of Mycobacteria Steering Committee.

Research into *M. avium* complex is supported through several grants and a P01 in NIAID.

Toxoplasma gondii (Recommendations 383–393)

Fundamental studies have been supported primarily through investigator-initiated research grants that are addressing issues related to the identification of parasite antigens and the genes coding for them, clonal virulence, heterogeneity in the parasite populations, host immune factors in the host–parasite interaction, and the impact of host genetic factors (including HLA) on disease expression. Studies are examining both acute infection and reactivation in the chronically infected host, especially toxoplasma encephalitis. Other studies are examining improved diagnostics and identification of novel combinations of drugs and immunomodulators. In addition, expanded support for translational research on development of immunologically based interventions has been provided through an RFA, "Immunologic Intervention in Infectious Diseases." Finally, support for development of vaccines against *T. gondii* is provided through the SBIR program.

Cryptosporidium and the Microsporidia (Recommendations 394–404)

Fundamental studies have been supported primarily through investigator-initiated research grants that are addressing issues related to virulence; heterogeneity in the parasite population; host resistance factors, including immune factors; and the impact of host genetic factors. In addition, because of the important role of *Cryptosporidium* infection in diarrheal disease of young children, epidemiologic studies are being carried out in endemic areas in both the Middle East and Brazil under the International Centers for Infectious Diseases Research Program. These studies should elucidate risk factors for transmission and identify potential models of intervention and prevention. Another aspect of these studies is the collection of information concerning potential isolate/strain differences. NIAID also has supported, through the SBIR program, development of novel immunologically based interventions targeted against *Cryptosporidium* and development of new diagnostics, including those for monitoring water supplies.

Future Actions

NIH will continue to incorporate the scientific priorities of the AIDS-associated OIs field in the development of the annual NIH Plan for HIV-Related Research. These priorities will be identified through the planned OAR-sponsored workshop on OIs as well as through ICD-specific initiatives.

NIH will continue to place a high priority on research on AIDS-associated OIs. Special initiatives in the form of PAs and RFPs are planned in FY 1997 and FY 1998 to target research on one or more of the OI pathogens. These initiatives include the issuance in FY 1997 by NIAID of RFPs entitled "Preclinical Evaluation of Therapies for *Pneumocystis carinii*," "Preclinical Evaluation of Therapies for *Cryptosporidium parvum*," "Preclinical Evaluation of Therapies for *Microsporidia*," and "Preclinical Evaluation of Therapies for *Mycobacterium avium*." In FY 1997, NIAID also plans to fund awards under PAs entitled "Innovative Drug Discovery Research in AIDS Opportunistic Infections" and "Collaborations for Advanced Strategies in Opportunistic Infections" to further stimulate research in this scientific area.

Special priority also will continue to be placed on TB research, and NIH will continue its collaboration with other PHS agencies in this area. NIAID maintains the Tuberculosis Working Group, which serves to coordinate TB-related research within the Institute as well as to maintain collaborations with other ICDs supporting research in this area. A PA is planned for FY 1998 that would support basic and drug discovery research for AIDS-associated OIs including TB and maintain the NCDDG-OI program.

VII. OPPORTUNISTIC INFECTIONS IN PEDIATRIC PATIENTS

Recommendation 405 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 31]

A specific focus on pediatric OIs is required, since there are both epidemiologic and microbiologic features that distinguish pediatric infections from those manifest in adulthood.

Recommendation 406 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 31]

Lengthened survival due to improvements in antiretroviral therapy and adjuvant measures should facilitate the study of acquisition, natural history, pathogenesis, and modes of intervention in OIs that are unique to pediatric HIV infection.

Recommendation 407 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 31]

Studies must be performed in children to better understand and treat infectious complications in this unique group of patients with AIDS.

Current Status

NIH agrees that there are unique pediatric manifestations of OIs and distinct scientific questions that need to be addressed in the pediatric population. NIH also strongly supports the recommendation that a special focus is needed to better define the pathogenesis of OIs in children and develop therapies to optimally prevent or treat these diseases. While therapeutic agents used to prevent or treat OIs in adults are also generally effective in children, development of pediatric formulations and pharmacokinetics as well as safety studies are required. In addition, for infections that are more commonly seen among infected children, studies to evaluate pediatric-specific approaches to prevention/treatment are needed. The PACTG has provided the major forum for evaluation of agents for prophylaxis and treatment of OIs in children, and pathogenesis-based research substudies have been incorporated into these clinical trials. In addition, various ICDs support basic science research on a number of specific infectious diseases through the R01 mechanism. Issues relating to the natural history of pediatric infections also have been conducted through ongoing NIH-funded epidemiologic studies (such as the WITS).

The PACTG has had an OI-specific scientific PACTG research advisory committee in place since 1990. Large Phase III trials have been restricted to studies of infections and/or treatments unique to pediatrics that, to date, have focused on therapies for prevention of recurrent serious bacterial infections. Because of the limited number of infected children with the “traditional” OIs seen in the adult population, the PACTG has concentrated on the conduct of Phase I/II safety and pharmacokinetics trials of new drugs, with the conduct of Phase III trials being generally performed in the adult population. Vaccine-preventable infections are important in pediatrics, and the safety and immunogenicity of several childhood vaccines are under study in the PACTG.

In order to track and analyze changing trends in infectious morbidity over time in HIV-infected children, the PACTG has been conducting a long-term outcome study of its trials’ participants

since 1993. In addition, the PACTG is collaborating with the CDC's Pediatric Spectrum of Disease Project.

Future Actions

Over the next several years, NIH will continue to evaluate agents against pediatric-specific OIs, focusing primarily on Phase I/II studies of new drugs for those infections with lower incidence in pediatrics and restricting Phase III trials to infections with significant incidence and impact in pediatric HIV infection. Pathogenesis-based questions will be addressed in the context of OI protocols in the PACTG and the traditional R01 grant mechanism.

NIH will continue to evaluate trends in pediatric OIs over time through ACTG 219 and natural history studies, as well as through collaborations with surveillance studies conducted by the CDC.

VIII. EMERGING/UNRECOGNIZED PATHOGENS

Recommendation 408 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 32]

The NIH needs to support broad-based innovative molecular and culture-based investigations to identify previously unrecognized opportunistic pathogens in HIV-infected persons. Certain unexplained clinical syndromes, such as those mentioned above, should be targeted. Particularly promising experimental approaches include consensus PCR amplification of conserved, phylogenetically useful microbial sequences (e.g., ribosomal DNA), and representational difference analysis (RDA). Careful selection of clinical samples and appropriate controls is critical (see the next recommendation). In the absence of proof of Koch's postulates, special attention should be placed upon data that support a causal association between molecular information and pathology. The NIH must recognize and accept the relatively high-risk nature of such investigations. Two-year, $150,000 to $200,000 pilot-feasibility grants may be a useful funding approach.

Please refer to the NIH responses to Recommendations 354–404.

Recommendation 409 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 33]

There is a need for the NIH to establish a clinical specimen bank (body fluids and tissues) from HIV-infected persons with designated syndromes of unknown but potentially infectious etiology. Specimens containing suspected pathogens, or isolates that resist identification should also be collected. The specimen bank(s) should include matched specimens as controls. The bank(s) would serve as repositories of samples for which qualified investigators could apply for access. Carefully procured and catalogued specimens of this type are difficult to secure and, as a widely available valuable resource, would encourage more numerous and productive investigations of new putative pathogens. The ACTG network might offer an attractive source of samples. For example, bronchoscopic, endoscopic, liver, lymph node, and whole blood samples might be identified, catalogued, and saved during the course of multicenter protocols. One of the advantages of a well-established network such as the ACTG is that critical clinical information and followup data would be available for correlation with molecular data. Actual, prospective "real-time" specimen collection will be necessary to track sporadic or unanticipated clinical syndromes; donor identification alone might be sufficient with later specimen collection for unexplained but common clinical syndromes.

Current Status

NIH does not support the recommendation that a clinical specimen bank should be established at NIH containing samples from HIV-infected persons with designated syndromes of unknown, but potentially infectious, etiology, because such an activity is the responsibility of the CDC. A

number of ICDs maintain repositories for biological specimens collected as part of ongoing epidemiologic studies of HIV-1 and clinical trials of agents to combat HIV-1 and its OI and neoplastic complications. The study participants who provide these specimens include patients manifesting a wide variety of HIV-related syndromes. Specimens from persons suffering from syndromes of unknown origin, as described above, may be identified through data linked to these specimens that can be used to describe the clinical conditions of the study participants in significant detail. One example of the utility of this arrangement came in investigating the phenomenon known as idiopathic CD4 lymphopenia (ICL), a condition identified when a group of individuals was discovered to have low CD4+ T-cell counts without testing positive for HIV-1. This discovery raised concerns about another etiology for AIDS; however, comprehensive studies of specimens from persons with ICL did not reveal any apparent "unknown" etiology that would make this phenomenon a truly discrete syndrome. The mechanisms for collecting and storing biological specimens and associated data that exist at present will be sufficient to address questions concerning the vast majority of clinical syndromes currently associated with HIV-1 infection, as well as questions likely to arise in the future. Attempts to establish additional clinical specimen banks based upon the premise of identifying, in a prospective manner, persons with "syndromes of unknown but potentially infectious etiology" would be extremely costly and inefficient and would be unlikely to accomplish the intended goals of such an effort.

Future Actions

ICDs will continue to collect biological specimens and associated clinical data from individuals participating in epidemiologic and clinical protocols in the manner detailed earlier in this document.

Recommendation 410 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 33]

> *The NIH should collaborate with and lend support to the CDC's Emerging Infections program. This program currently comprises four regional centers (in Connecticut, Minnesota, Oregon, and California) devoted to epidemiologic surveillance and analysis of unexplained critical illnesses and deaths in HIV-negative hosts. A similar network should be established for epidemiologic surveillance and laboratory investigation of unexplained critical illnesses and deaths in HIV-infected persons. The NIH should encourage this type of program for HIV-infected persons from regions of the world with high HIV endemicity.*

Current Status

NIAID and FIC are already coordinating and collaborating with CDC and other Federal agencies in the area of non-HIV-related emerging diseases. Among the avenues being pursued, are those made available through the National Science and Technology Council's Committee on International Science, Engineering, and Technology Policy and its various working groups. A recent example of such collaborations is the joint NIH/CDC cosponsorship of the International Scientific Colloquium on Ebola Virus Research held in September 1996 in Antwerp, Belgium, and hosted by the Institute of Tropical Medicine. CDC also assisted FIC and NIAID in the review of

supplemental proposals under a joint FIC/NIAID 1996 initiative in emerging infectious disease. One of the new 1996 awards was to a co-principal investigator working in a CDC-sponsored emerging diseases program in California. Further, FIC anticipates substantial coordination and possible collaboration with the CDC under its new International Training and Research Program in Emerging Infectious Diseases, which is modeled after AITRP.

Within the area of HIV/AIDS research, NIH, including FIC, has already taken important steps toward implementing this recommendation, particularly in regions of the world with high rates of HIV infection. This issue already is included in the natural history and epidemiology section of the NIH Plan for HIV-Related Research. The existence of various HIV subtypes is another related area receiving special emphasis under AITRP, as there is a concern that these subtypes could become endemic in the United States.

Future Actions

NIAID and FIC will continue to take the lead at NIH on this matter—NIAID from the perspective of research and FIC from the perspective of ensuring the necessary global scientific capacity to effectively deal with the issue. The OAR Coordinating Committee on Natural History and Epidemiology will be charged with responsibility for periodically monitoring and updating the NIH Plan for HIV-Related Research.

Recommendation 411 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 33]

> *There is a need to address the following issues regarding specific pathogens: KSHV—risk factors for infection and disease, reservoir, virus population structure, origins of the virus, mechanisms of transmission, incubation period, host immune response to infection and disease, and role in other diseases;* B. henselae*—mechanisms of transmission, geographic and temporal fluctuations in disease prevalence, and population structure;* Cyclospora*—relative importance as cause of chronic diarrhea in HIV-infected persons.*

Recommendation 412 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 34]

> *The NIH should fund basic laboratory investigations of pathogenic mechanisms used by recently identified opportunistic pathogens in HIV-infected persons.*

Recommendation 413 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 34]

> *Interactions between HIV and recently identified opportunistic pathogens should be explored. In addition, the contributions of one opportunistic microbial agent to the pathogenicity of another agent may be an important area for study.*

Recommendation 414 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 34]

> *The impact of HIV infection on the composition of the host commensal microbial flora should be evaluated as an important source of emerging pathogens.*

Recommendation 415 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 34]

The following issues should be addressed regarding specific pathogens: KSHV and B. henselae*—association of specific clones with angioproliferation or transformation, mechanisms of pathogen-associated angiogenesis or oncogenic transformation, mechanisms of cellular and tissue tropism, development of animal models, role of host cytokines and immune responses in causation of disease and host pathology, ability of a pathogen to modulate host responses; KSHV—development of methods for cultivation, assessment of latency;* B. henselae*—differential host tissue response in immunocompromised versus immunocompetent hosts.*

Recommendation 416 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 34]

The NIH should support efforts to develop novel and rapid methodologies for the detection and identification of opportunistic pathogens in HIV-infected persons.

Recommendation 417 [*Ad Hoc* Panel on OIs Research Subgroups Report, p. 35]

Regarding specific pathogens, the following issues should be addressed: KSHV—drug susceptibility, efficacy of foscarnet as therapy for KSHV infection; B. henselae*—antibiotic efficacy in cat scratch disease versus bacillary angiomatosis, appropriate duration of therapy.*

Please refer to the NIH responses to Recommendation 354–404.

Rosters

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Glossary

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Glossary

-A-

AACTG	Adult ACTG
ACTG	AIDS Clinical Trials Group
ACTU	AIDS Clinical Trials Unit
Add-HEALTH	National Longitudinal Study of Adolescent Health
AHCPR	Agency for Health Care Policy Research, DHHS
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Programs, FIC
AMB	AIDS Malignancy Bank, NCI
AMC	AIDS Malignancy Consortium, NCI
ARAC	AIDS Research Advisory Committee, NIAID
ARIS	AIDS Research Information System, OAR
ARP	Area Review Panel
ARR	AIDS-related research
ARRA	AIDS-Related Research Initial Review Group, Immunobiology Study Section 1 (formerly "A"), DRG
AVEG	AIDS Vaccine Evaluation Group, NIAID
AVRC	AIDS Vaccine Research Committee
AZT	azidothymidine or zidovudine (generic name)

-B-

Bishop-Calabresi Report	"A Review of the Intramural Program of the National Cancer Institute," a report by the *Ad Hoc* Working Group of the National Cancer Advisory Board, dated June 26, 1995, cochaired by J. Michael Bishop, M.D., and Paul Calabresi, M.D.
BIV	bovine immunodeficiency virus
B/START	Behavioral Science Training Award for Rapid Transition

-C-

CAB	Community Advisory Board
CAM	complementary and alternative medicine

Cassell-Marks Report	"Report of the Extramural Advisory Committee of the Director's Advisory Committee and the Implementation and Progress Report," Intramural Research Program, NIH, November 17, 1994, cochaired by Gail H. Cassell, Ph.D., and Paul A. Marks, M.D.
Cassman Report	"Report of the Working Group on the Division of Research Grants," chaired by Marvin Cassman, Ph.D., issued May 1995
CDC	Centers for Disease Control and Prevention, DHHS
CFAR	Center for AIDS Research
CMV	*cytomegalovirus*
CNS	central nervous system
Cochrane Collaboration	An international network of individuals and institutions that maintains and disseminates systematic reviews of randomized clinical trials in health care, McMaster University, Canada
COGs	Cooperative Oncology Groups, NCI
Cohort	a group of individuals with some characteristics in common
Coordinating Committees	OAR committees in major scientific areas responsible for developing the annual NIH Plan for HIV-Related Research
CPCRA	Terry Beirn Community Programs for Clinical Research on AIDS, NIAID
CRADA	Cooperative Research and Development Agreement
CRISP	Computer Retrieval Information Systems Program, a DRG database
CTA	Clinical Trial Agreements
CTEP	Clinical Therapeutics Evaluation Program, NCI
CTL	cytotoxic T lymphocytes
-D-	
DAIDS	Division of AIDS, NIAID
DAIT	Division of Allergy, Immunology, and Transplantation, NIAID
DATRI	Division of AIDS Treatment Research Initiative, NIAID
DCRT	Division of Computer Research and Technology, NIH
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID
DNA	deoxyribonucleic acid
DoD	Department of Defense
DPTDC	NIAID Preclinical Therapeutics Development Committee

DRG	Division of Research Grants, NIH
DTP	Developmental Therapeutics Program, NCI
DU	drug using
-E-	
EBV	Epstein-Barr virus
EEC	European Economic Community
EIAV	equine infectious anemia virus
-F-	
F31	Predoctoral Individual National Research Service Award
F32	See NRSA
FCRDC	Frederick Cancer Research and Development Center, NCI
FDA	Food and Drug Administration, DHHS
FIC	Fogarty International Center, NIH
FIRST	First Independent Research Support and Transition Award (R29)
FIV	feline immunodeficiency virus
FTE	full-time equivalent
FY	fiscal year
-G-	
GCRC	General Clinical Research Center, NCRR
-H-	
HCSUS	HIV Cost, Services, and Utilization Study
HHV	human herpesvirus
HIV-1	human immunodeficiency virus, type 1
HIV-2	human immunodeficiency virus, type 2
HIVIG	hyperimmune HIV immunoglobulin
HIVNET	HIV Vaccine Efficacy Trials Network: a network of domestic and international sites for trials of various prevention strategies, NIAID
HPV	human papillomavirus
HRSA	Health Resources and Services Administration, DHHS
HSV	herpes simplex virus
HTLV	human T-cell lymphotropic virus

-I-	
ICD	Institutes, Centers, and Divisions (NIH)
ICL	idiopathic CD4 lymphopenia
IDU	injection drug user
IMPAC	Information for Management Planning, Analysis, and Coordination: a database system utilized by NIH and other Federal agencies
IND	investigational new drug
IOM	Institute of Medicine, National Academy of Sciences
IRG	Initial Review Group: study section within DRG
IRPG	Interactive Research Project Grant
-J-	
JCV	a human polyomavirus (initials of patient from whom first isolated)
-K-	
K01	Research Scientist Development Award for Research and Training
K08	Clinical Investigator Award
K11	Physician Scientist Award (individual)
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
-L-	
LRP	Loan Repayment Program (NIH)
-M-	
M01	a GCRC grant program
MACS	Multicenter AIDS Cohort Study, NIAID
memantine	m-methyl d-asparate
MERIT Award	Method to Extend Research in Time Award (R37)
MESH	medical subject headings
MSM	men who have sex with men
-N-	
NARC	Neurologic AIDS Research Consortium, NINDS
NAVTF	National AIDS Vaccine Task Force (proposed)
NCDDG	National Cooperative Drug Discovery Group, NIAID

NCI	National Cancer Institute, NIH
NCRR	National Center for Research Resources, NIH
NCVDG	National Cooperative Vaccine Development Group, NIAID
NEI	National Eye Institute, NIH
NEP	needle/syringe exchange programs
NHL	non-Hodgkin's lymphoma
NHLBI	National Heart, Lung, and Blood Institute, NIH
NIA	National Institute on Aging, NIH
NIAAA	National Institute on Alcohol Abuse and Alcoholism, NIH
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH
NICHD	National Institute of Child Health and Human Development, NIH
NIDA	National Institute on Drug Abuse, NIH
NIDCD	National Institute on Deafness and Other Communication Disorders, NIH
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases, NIH
NIDR	National Institute of Dental Research, NIH
NIGMS	National Institute of General Medical Sciences, NIH
NIH	National Institutes of Health, DHHS
NIMH	National Institute of Mental Health, NIH
NINDS	National Institute of Neurological Disorders and Stroke, NIH
NINR	National Institute of Nursing Research, NIH
NRSA	National Research Service Award (F32)
-O-	
OAR	Office of AIDS Research, NIH
OARAC	OAR Advisory Council
OAM	Office of Alternative Medicine, NIH
OER	Office of Extramural Research, NIH
OI	opportunistic infection
ORMH	Office of Research on Minority Health, NIH

-P-

P01	Research Program Project
P30	Center Core Grant
P50	Specialized Center (for research program projects)
P51	Primate Research Center Grant
PA	Program Announcement
PACTG	Pediatric ACTG
PCP	*Pneumocystis carinii* pneumonia
PCR	polymerase chain reaction
PHS	Public Health Service, DHHS
PI	principal investigator
PNS	peripheral nervous system
PROG	peer-review oversight group
PSWG	Prevention Science Working Group

-R-

R01	investigator-initiated research project
R03	Small Research Grant
R21	Exploratory/Developmental Grant
R29	*see* FIRST
R55	James A. Shannon Director's Award
RCMI	Research Centers at Minority Institutions Award
RCT	randomized clinical trials
RFA	Request for Applications (using R01 funding mechanisms or U01 cooperative agreements)
RFP	Request for Proposals (using N01 funding mechanisms or contracts)
RNA	ribonucleic acid
RNase	ribonuclease
RPG	Research Program Grant
RPRC	Regional Primate Research Center, NCRR
RT	reverse transcriptase, a retroviral enzyme

-S-	
SAMHSA	Substance Abuse and Mental Health Services Administration, DHHS
SBIR	Small Business Innovative Research program
SCID	severe combined immunodeficiency mouse
SEP	Special Emphasis Panel
SHIV	a chimera of SIV and HIV-1
SIV	simian immunodeficiency virus
SOCA	Studies of the Ocular Complications of AIDS, NEI
SPF	specific pathogen free
SPIRAT	Strategic Program for Innovative Research on AIDS Therapies, NIAID
SRA	Scientific Review Administrator
STD	sexually transmitted disease
STTR	Small Business Technology Transfer program, NIH
SVEUs	Simian Vaccine Evaluation Units, NIAID
-T-	
TB	tuberculosis
T. gondii	*Toxoplasma gondii*
-U-	
U01	Research Project (cooperative agreements)
U19	Research Program (cooperative agreements)
UNAIDS	United Nations Joint Programme on AIDS
USAID	U.S. Agency for International Development, State Department
-V-	
VA	Department of Veterans Affairs
VDEG	Vaccine Design and Evaluation Group, NIAID
VZV	varicella-zoster virus
-W-	
WHO	World Health Organization, United Nations
WIHS	Women’s Interagency HIV Study
WITS	Women and Infants Transmission Study, NIAID

WRAIR	Walter Reed Army Institute of Research, DoD

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NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
NIH AIDS RESEARCH PROGRAM EVALUATION WORKING GROUP REPORT	**Working Group Report**		
I. INVESTIGATOR-INITIATED RESEARCH ***Increase support for and improve peer review of investigator-initiated research***			
1. The proportion of the NIH AIDS research budget allocated to support unsolicited investigator-initiated research should be approximately doubled.	Working Group Report pg. 6	**1 pg. 13**	
2. Selected members of AIDS-related IRGs should participate in the OAR's process for setting research priorities. As an integral part of the IRG process, these individuals, in concert with DRG and OAR staff, should familiarize their IRG members with the OAR- and ICD-defined AIDS research priorities.	Working Group Report pg. 6	**2 pg. 13**	
3. Scientific Review Administrators of AIDS-related IRGs should be included as members of the OAR Coordinating Committees corresponding to their area of expertise.	Working Group Report pg. 6	**3 pg. 13**	**2 pg. 13**
4. The OAR, in concert with the ICDs, should inform the ICD advisory bodies and councils of the NIH AIDS research priorities as outlined in the NIH Plan for HIV-Related Research.	Working Group Report pg. 6	**4 pg. 13**	**2 pg. 13**
5. The OAR should develop a strategy to distribute the NIH Plan for HIV-Related Research to the scientific community and other interested parties.	Working Group Report pg. 6	**5 pg. 14**	**2 pg.13**
6. AIDS-related grant proposals should include a discussion of how the proposed investigation relates to the research priorities detailed in the NIH Plan for HIV-Related Research.	Working Group Report pg. 6	**6 pg. 15**	
7. It is critical that the DRG work with OAR and the ICDs to provide IRGs with high-caliber, mature, and diverse scientists and clinicians. DRG should investigate possible mechanisms to ensure high-quality reviews responsive to the changing scientific issues. Such mechanisms might include working with learned societies to identify distinguished scientists with a broad range of expertise to serve on IRGs, making greater use of voting *ad hoc* members, and exercising flexibility on the term limits for IRG participation.	Working Group Report pg. 7	**7 pg. 16**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
8. DRG should be responsive to the evolving character of AIDS research and modify IRG composition or define new IRGs as needed. The Working Group believes that the existing AIDS-related IRGs should be redefined and reconfigured to reflect the current scientific priorities for AIDS research, particularly as they relate to vaccine and prevention science research needs.	Working Group Report pg. 7	**8 pg. 17**	
9. Given the crucial importance of training for the research enterprise, the OAR should establish a Coordinating Committee on Training and Infrastructure, with the same responsibilities as other OAR Coordinating Committees.	Working Group Report pg. 8	**9 pg. 17**	
10. OAR Coordinating Committee on Training and Infrastructure should review the NIH Plan for HIV-related research and address a wider range of NIH training mechanisms (such as the K awards, supplements, and predoctoral research opportunities). The Plan should include strategies for the systematic outcome evaluation of training awards.	Working Group Report pg. 8	**10 pg. 18**	**9 pg. 17**
11. Innovative mechanisms to provide short-term (2-3 year) support of young investigators at levels sufficient to initiate quality research programs should be developed.	Working Group Report pg. 8	**11 pg. 18**	
12. Many investigator-initiated research grants in areas unrelated to HIV/AIDS objectives, held by distinguished senior scientists, generate findings that may be relevant to questions in AIDS research. To encourage these laboratories to explore AIDS-related avenues of research, a program should be established that offers supplemental funding to support postdoctoral fellows or graduate students to carry out AIDS-related research.	Working Group Report pg. 9	**12 pg. 21**	
13. NIH should develop programs for AIDS-related research training explicitly tailored and targeted to ethnic minority individuals, primarily at the postdoctoral level. Rather than simply supplementing existing grants, these programs should involve collaborative mentoring activities in research projects defined by the minority scientists. Programs should include intense and long-term mentoring and support in the NIH grant application process. A criterion of evaluation of these programs should be the number of new NIH-funded principal investigators (PIs) of ethnic minority background.	Working Group Report pg. 9	**13 pg. 22**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
14. OAR should investigate the possibility of extending the AIDS Loan Repayment Program (LRP) to forgive student loan debts for postdoctoral fellows working in AIDS research outside of the NIH intramural program.	Working Group Report pg. 9	**14 pg. 23**	
II. AIDS VACCINE RESEARCH *Establish a restructured trans-NIH vaccine research effort*			
1. The entire AIDS vaccine research effort of the NIH should be restructured. A trans-NIH vaccine program should be established with leadership and oversight provided by distinguished, non-Government scientists.	Working Group Report pg. 10	**15 pg. 25**	
2. A National AIDS Vaccine Task Force (NAVTF), chaired by the Director of OAR, should be established in the White House Office of the National AIDS Policy, with responsibility for coordinating all Government-sponsored vaccine programs.	Working Group Report pg. 11	**16 pg. 26**	
3. NIAID, in partnership with other ICDs with complementary expertise, should promptly develop a comprehensive plan for HIVNET's organization, Governance, research, and funding. This plan should be reviewed in 1996 by a joint OAR/ICD-convened panel of extramural experts in behavioral, social, epidemiological, prevention, pathogenesis, and treatment research as well as vaccine research. If reviewers determine that there are significant deficiencies in the plan, funds could be released for retargeting to other essential areas of AIDS research.	Working Group Report pg. 12	**17 pg. 27**	
III. RESEARCH ON THE HUMAN IMMUNE SYSTEM *Augment research efforts to better understand the human immune system*			
1. OAR should convene a series of workshops of expert immunologists to develop a plan to accelerate progress in understanding the following: • **The basic biology and development of human immunocompetent cells and of the unique aspects of the physiology of the human immune system.** • **How HIV or SIV perturbs the human or primate immune system to impair the function of and destroy immunocompetent cells.** • **Why normal replacement mechanisms are unable to restore a functional immune system in infected individuals.** • **Why normal host defenses are unable to ultimately contain HIV infection.**	Working Group Report pg. 13	**18 pg. 29**	

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
2.	**NIH should increase support for research of the human immune system by traditional mechanisms of investigator-initiated research and intramural projects.**	Working Group Report pg. 13	**19 pg. 29**	
3.	**NIH should facilitate interactions between basic immunologists and AIDS researchers through consortial approaches. Anticipated benefits of the consortial mechanism include overcoming basic immunologists' unfamiliarity with AIDS research and concerns about working with infectious agents; facilitating the exchange of ideas, techniques, reagents, and personnel; and increasing the likelihood that postdoctoral fellows enter AIDS research.**	Working Group Report pg. 13	**20 pg. 31**	
IV.	**HIV PREVENTION SCIENCE RESEARCH** ***Develop a comprehensive HIV Prevention Science Agenda***			
1.	**NIH, acting through the OAR, should develop a coordinated and comprehensive Prevention Science Agenda that includes and combines biomedical, behavioral, and social interventions. This agenda should begin with an NIH-wide plan that then is integrated where possible with similar plans at the Centers for Disease Control and Prevention (CDC) and other relevant Federal agencies.**	Working Group Report pg. 15	**21 pg. 33**	
2.	**NIH should convene an HIV Prevention Science Advisory Committee reporting to the Director of OAR.**	Working Group Report pg. 15	**22 pg. 33**	**21 pg. 33**
3.	**OAR should appoint an HIV Prevention Science Coordinator charged with coordinating the implementation of the Prevention Science Agenda.**	Working Group Report pg. 15	**23 pg. 33**	**21 pg. 33**
4.	**NIH IRGs for the review of AIDS research grants should be reconfigured to include one with appropriate expertise in and responsibility for HIV prevention science proposals (including cross-disciplinary studies).**	Working Group Report pg. 15	**24 pg. 35**	**8 pg. 17**
V.	**CLINICAL TRIALS** ***Integrate all adult clinical trial programs into a single network***			
1.	**A single integrated adult clinical trials network should be created with primary sponsorship from NIAID and ancillary funding from other Institutes involved in clinical trials.**	Working Group Report pg. 17	**25 pg. 36**	
2.	**A uniform standard for clinical trials databases should be developed to ensure that data can be shared between studies both within and across trials programs.**	Working Group Report pg. 18	**26 pg. 36**	

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
3.	**The Working Group recommends an early reexamination of the optimal approach to future pediatric AIDS clinical trials. Furthermore, significant reductions in allocations to the PACTG are recommended. These should be implemented in such a manner so that the essential clinical trials function of the PACTG is not impaired.**	Working Group Report pg. 19	**27 pg. 38**	
4.	**An oversight committee for all NIH-sponsored AIDS clinical trials should be created that is based in the OAR and includes broad scientific and community representation.**	Working Group Report pg. 19	**28 pg. 40**	
VI.	**DRUG DISCOVERY RESEARCH** ***Refocus and restructure the drug discovery research effort***			
1.	**An external scientific advisory board, including a representative from OAR, should be constituted to provide guidance regarding appropriate goals for future DTP AIDS research activities. Future assessment of the DTP AIDS drug discovery program should include its ability to support the overall NIH drug discovery effort for HIV and for the anti-OI discovery efforts of other ICDs. NCI bears a particular responsibility for the development of novel treatments for AIDS-associated malignancies. To accomplish these goals, DTP management and structure require careful review, both to determine what can be eliminated from the AIDS drug discovery effort and to appropriately assign the funds allotted to AIDS-directed research. A substantial decrease in the size and funding of the DTP's current AIDS-related drug discovery effort is appropriate.**	Working Group Report pg. 21	**29 pg. 42**	**300 pg. 257**
VII.	**RESEARCH ON OPPORTUNISTIC INFECTIONS** ***Augment basic science research on AIDS-associated opportunistic infections and facilitate transfer of new findings to early clinical evaluation***			
1.	**Reinvigorate the basic science research effort on AIDS-associated opportunistic infections, emphasizing studies of fundamental aspects of the biology of the responsible microorganisms and the mechanisms of disease pathogenesis.**	Working Group Report pg. 22	**30 pg. 44**	
2.	**The NIH should pursue innovative approaches, such as enhancing the quality and AIDS focus of the Small Business Innovative Research (SBIR) grant program, to foster the transfer of new laboratory findings to early "proof of concept" clinical evaluation.**	Working Group Report pg. 23	**31 pg. 45**	

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VIII. COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) RESEARCH ***Strengthen the scientific base for the assessment of complementary and alternative medicine (CAM) therapies for HIV disease***			
1. The OAR should establish an *ad hoc* advisory group to communicate community interest in the area of CAM therapies for HIV disease and to help identify therapies with apparent promise or potential danger for persons with HIV infection. This advisory group should consist of scientists experienced in clinical and laboratory evaluation of candidate therapies for HIV infection or its complications, and community representatives, including individuals who use CAM therapies.	Working Group Report pg. 24	**32 pg. 48**	
2. A catalog should be prepared of all research relating to HIV-related CAM therapies currently being supported by the NIH. OAR and its *ad hoc* advisory group should work with the OAM to establish an operational definition of CAM therapy as it relates to HIV disease and to construct a taxonomy to categorize CAM therapies in this area.	Working Group Report pg. 24	**33 pg. 48**	
3. The OAR and its *ad hoc* advisory group should work with the OAM to sponsor a workshop on the research methodology for the evaluation of the efficacy of CAM therapies for HIV disease. The OAR also should work with the OAM to sponsor workshops to educate individuals interested in the evaluation of candidate CAM therapies for HIV disease about the preparation of NIH grant applications and the processes by which such applications are evaluated.	Working Group Report pg. 24	**34 pg. 49**	
4. The OAR should work with the OAM and DRG to suggest individuals to serve as *ad hoc* members of IRGs that are reviewing HIV CAM therapy research proposals. Criteria for the selection of such members should include those currently utilized by DRG to select IRG members, as well as experience in the scientific evaluation of novel therapeutic approaches and knowledge of the concepts and practices of CAM therapies.	Working Group Report pg. 25	**35 pg. 49**	
IX. REGIONAL PRIMATE RESEARCH CENTERS ***Reorganize procedures to ensure that Centers are available and responsive to non-Center-affiliated scientists***			

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
1. The OAR should commission a panel to define optimal mechanisms to support AIDS research at the RPRCs and to devise strategies that permit the most promising research ideas to be tested.	Working Group Report pg. 26	**36 pg. 50**	
2. The process for competition of NCRR AIDS supplemental funding should be opened up to all extramural investigators.	Working Group Report pg. 26	**37 pg. 51**	
3. To optimize the quality and productivity of AIDS research conducted at the RPRCs, the NCRR IRGs that review the Centers should be strengthened by the addition of scientists with expertise in AIDS and AIDS-related research.	Working Group Report pg. 27	**38 pg. 52**	
4. Open competition for funds to support relevant animal costs included in DRG-reviewed grants might be accomplished through a regularly recurring RFA.	Working Group Report pg. 27	**39 pg. 53**	
X. AIDS RESEARCH CENTERS ***Strengthen AIDS Research Centers to promote multidisciplinary research on the disease***			
1. The Working Group recommends that funding for the CFAR program as a whole be increased by approximately 50 percent. This would allow annual funding in the range of $750,000 to $1.5 million per year, to be allocated in proportion to a Center's research capacity and its ability to build an interdisciplinary research program and attract R01s.	Working Group Report pg. 28	**40 pg. 55**	
2. The comprehensive research centers program, funded by NIMH, has been found to be productive and should be maintained.	Working Group Report pg. 29	**41 pg. 55**	
XI. REPOSITORIES AND DATABASES ***Ensure that central repositories of biomedical specimens and databases are of the highest quality and accessible to qualified investigators***			
1. Improvements should be made in repositories and databases in accord with three principles: repositories and databases should be investigator-designed and hypothesis-driven; accessible to all qualified investigators; and coordinated under a new user-friendly central tracking system maintained under the auspices of the OAR. Support should be provided for collection of specimens, as dictated by scientific needs, and for these repositories and databases.	Working Group Report pg. 30	**42 pg. 57**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
XII. AIDS RESEARCH INFORMATION SYSTEM ***Upgrade the NIH AIDS Research Information System and increase the information base***			
1. A new information database system should be developed containing grant, contract, or intramural project titles and numbers; names of principal investigator and institutional affiliations; budget amounts; funding ICDs; and an abstract for each proposal. In addition, the Working Group recommends that a yearly summary abstract of ongoing activities and list of publications resulting from each award be prepared by the principal investigator and included in the database. The database should contain this information for every project coded by the ICDs as AIDS or AIDS-related.	Working Group Report pg. 31	**43 pg. 62**	
XIII. DEFINITIONS OF AIDS AND AIDS-RELATED RESEARCH ***Develop and implement a clear definition of AIDS and AIDS-related research through an evolving process***			
1. The Working Group has determined that a substantial proportion of NIH AIDS funds has been previously and is presently inappropriately classified as AIDS or AIDS-related by many ICDs. Such funds should be redirected to research programs appropriately classified as AIDS and AIDS-related. It is recognized that an orderly plan for redirection is needed and that its implementation may require a period of time.	Working Group Report pg. 33	**44 pg. 65**	
2. The Working Group strongly recommends that the OAR, in cooperation with the ICDs, develop guidelines/ criteria for the classification and coding of projects as AIDS and AIDS-related. Such a coding system should be implemented immediately to permit multiyear analyses of projects by these categories. The Working Group recognizes that these guidelines may evolve as AIDS research priorities change. It is crucial that this coding system be developed to ensure that AIDS research funds are effectively, efficiently, and optimally utilized.	Working Group Report pg. 33	**45 pg. 65**	**44 pg. 65**
3. AIDS funds should continue to support excellent work in selected underdeveloped areas of basic research judged to be likely to make substantial contributions to progress against this disease and its sequelae. The research areas for potential investment should be clearly identified in the annual NIH Plan for HIV-Related Research so that they can be targeted for NIH-wide additional support.	Working Group Report pg. 34	**46 pg. 66**	

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XIV. OFFICE OF AIDS RESEARCH ***Preserve a strong OAR to provide leadership and coordination to the entire NIH AIDS research program***			
1. The OAR should immediately develop a plan to implement the recommendations in this evaluation report.	Working Group Report pg. 35	**47 pg. 67**	
NATURAL HISTORY, EPIDEMIOLOGY, AND PREVENTION RESEARCH AREA REVIEW PANEL	**Natural History, Epidemiology, and Prevention Research**		
I. Executive Summary **1. Develop an HIV Prevention Science Strategy for the National Institutes of Health (NIH), coordinated by the Office of AIDS Research (OAR).**	Natural History, Epidemiology,and Prevention Research pg. 2	**48 pg. 71**	**21 pg. 33**
2. Integrate the NIH HIV Prevention Science Strategy into a U.S. Prevention Plan coordinated by the Department of Health and Human Services (DHHS) and involving all relevant Agencies and Departments.	Natural History, Epidemiology, and Prevention Research pg. 2	**49 pg. 71**	**21 pg. 33**
3. Take an active role in designing a comprehensive International Prevention Science Agenda that builds on the U.S. Prevention Plan and provides for the financial support and scientific expertise necessary to meet challenges in HIV/AIDS research at the international level.	Natural History, Epidemiology, and Prevention Research pg. 2	**50 pg. 71**	**21 pg. 33**
4. Define how mucosal HIV shedding and transmission are influenced by factors such as viral subtype, local immune responses, cervical ectopy in adolescent and young women, HIV infection stage, antiretroviral treatment, and vaccines.	Natural History, Epidemiology, and Prevention Research pg. 3	**51 pg. 71**	
5. Conduct interdisciplinary prevention trials of the full range of promising biomedical and social and behavioral interventions to prevent HIV transmission. For example, evaluate topical microbicides, investigate new approaches to improve the effectiveness of syringe- and needle-exchange and other methods of distributing sterile syringes and needles, and evaluate a full range of approaches to preventing perinatal transmission, such as chemoprophylaxis and immunoprophylaxis as well as low-cost alternatives such as intrapartum antisepsis and nutritional supplementation.	Natural History, Epidemiology, and Prevention Research pg. 3	**52 pg. 72**	
6. Identify features of sexual and social networks that determine rates of sexual and perinatal HIV transmission.	Natural History, Epidemiology, and Prevention Research pg. 3	**53 pg. 73**	

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7.	**In close collaboration with scientists studying immunology and pathogenesis, plan and perform interdisciplinary cohort studies of HIV-infected persons with unusual outcomes to elucidate responsible mechanism(s) and identify potentially modifiable risk factors, including opportunistic infections (OIs) and OI prevention, that significantly affect the rate of disease progression.**	Natural History, Epidemiology, and Prevention Research pg. 4	**54 pg. 74**	
8.	**Recruit high-risk HIV-uninfected cohorts in order to study early diagnosis and treatment of early HIV infection and the influence of particular early immunologic and virologic events on subsequent disease course.**	Natural History, Epidemiology, and Prevention Research pg. 4	**55 pg. 75**	
9.	**Develop measures for preventing exposure to opportunistic pathogens and evaluate these measures as they affect the development of OIs in HIV-infected persons. Also evaluate the effect of preventing opportunistic diseases (through preventing exposure to OI pathogens and through primary and secondary prophylaxis) on progression of HIV-mediated immunosuppression.**	Natural History, Epidemiology, and Prevention Research pg. 4	**56 pg. 76**	**354-404 pgs. 297-305**
10.	**Continue to characterize the full spectrum of illness in certain populations of special interest, including HIV-infected or HIV-exposed infants and children, adolescents infected with HIV, international populations with infections of varying HIV subtypes or clades, and persons in traditional risk groups with unique co-exposures, such as infection with the Kaposi's sarcoma (KS)-associated herpes virus.**	Natural History, Epidemiology, and Prevention Research pg. 4	**57 pg. 76**	
II. **A.**	**Subpanel Reports** **Sexual Transmission Subpanel Report**			
A1	**Define how mucosal HIV shedding and transmission are influenced by viral subtype, local immune responses, cervical ectopy (in adolescent and young women), HIV infection stage, antiretroviral treatment, and experimental vaccines. Identify factors such as genetic and immunologic parameters associated with host susceptibility or resistance.**	Natural History, Epidemiology, and Prevention Research pg. 15	**58 pg. 78**	**51 pg. 71**
A2	**Continue and broaden ongoing intervention trials on such factors as topical microbicides and early diagnosis and treatment of STDs, and consider appropriate designs for innovative prevention research on such potentially important factors as cervical ectopy, circumcision, and hormonal contraception.**	Natural History, Epidemiology, and Prevention Research pg. 15	**59 pg. 78**	**52 pg. 72**

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
A3	**Identify the social and ecologic determinants, including sexual and social networks, that account for variations in the distribution of infection and disease, including the role of demographic factors such as socioeconomic status, race, ethnicity, and age.**	Natural History, Epidemiology, and Prevention Research pg. 15	**60 pg.78**	**53 pg. 73**
A4	**Develop rapid, inexpensive, and simpler diagnostic tests for STDs to facilitate treatment, thereby strengthening prevention and control of HIV and STDs.**	Natural History, Epidemiology, and Prevention Research pg. 15	**61 pg. 78**	
B.	**Perinatal/Postnatal Transmission Subpanel Report**			
B1	**Develop modalities to minimize perinatal transmission that extend benefits of chemoprophylaxis, including hyperimmune globulin and combination chemotherapies.**	Natural History, Epidemiology, and Prevention Research pg. 17	**62 pg. 79**	
B2	**Evaluate low-cost prevention strategies for resource-poor settings, such as intrapartum antisepsis, short-course antiretroviral prophylaxis, vitamin supplementation, and shortened duration of breast-feeding.**	Natural History, Epidemiology, and Prevention Research pg. 17	**63 pg. 80**	
B3	**Design and test behavioral and social intervention strategies specifically for HIV-infected, pregnant women regarding therapies to reduce vertical HIV transmission.**	Natural History, Epidemiology, and Prevention Research pg. 17	**64 pg. 81**	
B4	**Determine the long-term effects of *in utero* exposure to HIV and antiretroviral prophylaxis, including the emergence of drug resistance in both HIV-infected mothers and infants.**	Natural History, Epidemiology, and Prevention Research pg. 17	**65 pg. 83**	**27 pg. 38**
C.	**Parenteral/Injection Drug Use Transmission Subpanel Report**			
C1	**Conduct prevention studies, including RCTs, to assess how increasing access to sterile syringes via syringe-exchange programs, retail pharmacy sales, and other methods affects HIV transmission and drug use behaviors.**	Natural History, Epidemiology, and Prevention Research pg. 18	**66 pg. 83**	
C2	**Evaluate the social, cultural, and economic factors, including social networks, that influence specific drug-using practices (including injection of various drugs) and the prevalence and incidence of HIV infection among drug users.**	Natural History, Epidemiology, and Prevention Research pg. 19	**67 pg. 84**	
C3	**Investigate interactions of IDU and IDU-related behaviors on viral load, viral subtype, and viral shedding.**	Natural History, Epidemiology, and Prevention Research pg. 19	**68 pg. 85**	

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
C4	**Conduct research necessary for the development of new methods for the decontamination of syringes and other drug use equipment, including research on the survival and transmissibility of HIV on IDU paraphernalia.**	Natural History, Epidemiology, and Prevention Research pg. 19	**69 pg. 86**	
D.	**Natural History/Disease Progression Subpanel Report**			
D1	**Perform interdisciplinary studies of HIV-infected persons with unusual outcomes, including rapid progressors, nonprogressors, and persons with persistently low CD4 counts in the absence of clinical disease.**	Natural History, Epidemiology, and Prevention Research pg. 21	**70 pg. 87**	**54 pg. 74**
D2	**Identify factors that significantly affect the rate of disease progression and amount of viral shedding that could be useful to the development of new interventions.**	Natural History, Epidemiology, and Prevention Research pg. 21	**71 pg. 87**	**51 pg. 71**
D3	**Recruit high-risk HIV-uninfected cohorts in order to study early diagnosis and treatment of infection, the effects of particular immunologic and virologic characteristics at the time of infection on long-term disease course, and the correlates of protection among multiexposed persistently uninfected persons.**	Natural History, Epidemiology, and Prevention Research pg. 21	**72 pg. 87**	**55 pg. 75**
D4	**Identify biological and sociobehavioral risk factors for OIs and evaluate the potential of targeting these risk factors in preventive interventions.**	Natural History, Epidemiology, and Prevention Research pg. 21	**73 pg. 88**	
D5	**Continue to characterize the full spectrum of illness on certain populations of special interest, including HIV-exposed or HIV-infected infants, children, and adolescents; international populations with infections of varying HIV subtypes or clades; and persons from all risk groups with unique co-exposures, such as infection with the KS-associated herpes virus.**	Natural History, Epidemiology, and Prevention Research pg. 21	**74 pg. 88**	**57 pg. 76**
E.	**Methodology Subpanel Report**			
E1	**Use methodologic guidelines for HIV prevention trials research analogous to the trial-phasing system in pharmaceutical research, ensuring an orderly sequence of prevention studies, from the identification of potentially modifiable risk factors for HIV transmission to the identification and evaluation of interventions to interrupt transmission and the systematic application of research results in well-defined populations.**	Natural History, Epidemiology, and Prevention Research pg. 23	**75 pg. 89**	**77 pg. 90**

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
E2	**Require and support the rigorous study designs essential in HIV prevention research. This may require levels of funding comparable to those used in clinical trials of pharmaceuticals, and the NIH should provide the levels of support necessary to conduct such research.**	Natural History, Epidemiology, and Prevention Research pg. 23	**76 pg. 89**	**75 pg. 89**
E3	**Support a comprehensive program of interdisciplinary methodologic research on the statistical design and analysis of community randomized HIV-prevention trials and on field studies and theoretical models of the role of social networks in HIV transmission.**	Natural History, Epidemiology, and Prevention Research pg. 23	**77 pg. 90**	**75 pg. 89**
E4	**Develop guidelines for systematic structured reporting of HIV prevention research studies that are analogous to those now required by many journals for reports of clinical trials, and establish and sponsor a collaborative prevention trials review and evaluation group (a Cochrane Collaborative Group) to maintain the database and continually monitor and assess the state of HIV prevention research.**	Natural History, Epidemiology, and Prevention Research pg. 24	**78 pg. 91**	
III-IV.	**Review of Natural History, Epidemiology, and Biomedical Prevention Research at the NIH by Institute and Center**			
A. **1** **2** **3** **4**	**National Institute of Allergy and Infectious Diseases (NIAID)** **Redirect NHEBP funding within the clinical trials networks to evaluate the effects of antiretroviral therapy on mucosal shedding of HIV.** **Review studies of seropositive or seronegative cohorts periodically by a multidisciplinary panel of experts to ensure that all opportunities for productive and high-priority research are adequately addressed. Such reviews should be coordinated by the OAR to facilitate inter-Institute cooperation.** **Augment the epidemiologic expertise of cohort study investigators by recruiting investigators with expertise in basic, clinical, social, and behavioral sciences. The need for multidisciplinary research teams extends to investigators using repository specimens.** **The NIAID Centers for AIDS Research Program should include the investigation of epidemiology, natural history, and prevention as a specific aim, with the goal of increasing benefit to public health.**	Natural History, Epidemiology, and Prevention Research pg. 28	**79 pg. 93**	**40 pg. 55**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
B. National Heart, Lung, and Blood Institute (NHLBI) **1 Transfer funds currently supporting developmental investigations of artificial blood substitutes and research on the safety of the blood supply to other high-priority areas in biomedical prevention and epidemiology.** **2 Review ongoing pathogenesis studies of cardiopulmonary and hematologic complications of HIV infection for opportunities to include prevention components within the protocols and link them with initiatives from other ICDs involved in related efforts.** **3 Accelerate plans to publicize the availability of potentially valuable biologic materials in repositories from studies of transfusion-associated HIV infection.**	Natural History, Epidemiology, and Prevention Research pg. 29	**80** **pg. 96**	
C. National Institute of Child Health and Human Development (NICHD) **1 Shift perinatal HIV resources from domestic transmission studies to international prevention studies.** **2 Increase the use of experimental trials and multicenter collaborations to evaluate the influence of contraceptives on STD/HIV transmission. Utilize the contraceptive clinical trials network and RCTs where feasible.**	Natural History, Epidemiology, and Prevention Research pg. 30	**81** **pg. 98**	
D. National Institute on Drug Abuse (NIDA) **1 Take a leading role in conducting and coordinating programs of research on ways to prevent HIV by facilitating access to sterile syringes, on the social ecology of parenteral HIV transmission, and on social-structural or policy factors that may affect initiation of drug injection.** **2 Investigate interactions of drug and drug-related behaviors on viral type, viral load, and shedding in order to determine the effects on transmission and disease progression in HIV-infected drug users.**	Natural History, Epidemiology, and Prevention Research pg. 31	**82** **pg. 101**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
E. National Cancer Institute (NCI) **1 Focus on epidemiologic research of AIDS-related and retroviral-associated cancers.** **2 As opportunities develop, pursue intervention research with other groups within and outside of the NIH that already have established the necessary multidisciplinary research teams.** **3 Actively pursue expanded linkages to cohorts funded by other ICDs to maximize opportunities to study HIV-associated malignancies.**	Natural History, Epidemiology, and Prevention Research pg. 33	**83** **pg. 102**	
F. National Institute of Mental Health (NIMH) **1 In collaboration with behavioral and social scientists, continue the spectrum of research from observational studies to randomized controlled trials directed at primary prevention of HIV transmission, with an emphasis on targeting special at-risk populations, maintaining of behavior change, and assessing of both biological as well as behavioral outcomes.** **2 In collaboration with behavioral and social scientists, expand current research on social and behavioral factors that affect the rate of HIV disease progression, especially among persons with unusual HIV outcomes.**	Natural History, Epidemiology, and Prevention Research pg. 35	**84** **pg. 104**	
G. Fogarty International Center (FIC) **1 The FIC program warrants continued support in establishing linkages between U.S. universities and scientists in other countries for prevention research. Increased support linked to a U.S. institution is needed for reentry research funding for high-caliber trainees.**	Natural History, Epidemiology, and Prevention Research pg. 36	**85** **pg. 107**	
V. Special Issues **A. Funding Mechanisms–Extramural and Intramural Research**			
A1 Continue OAR and ICD support of directed types of funding mechanisms in the area of natural history and epidemiology, particularly the use of cooperative agreements in the areas where central coordination is necessary. Directed funding should be provided for research in high-priority areas where intellectual or financial incentives are not sufficient to attract significant scientific interest.	Natural History, Epidemiology, and Prevention Research pg. 38	**86** **pg. 108**	
A2 Provide support and oversight for the Centers for AIDS Research programs that include biomedical, clinical, laboratory, and prevention science research.	Natural History, Epidemiology, and Prevention Research pg. 38	**87** **pg. 109**	**40, 41** **pg. 55**

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
A3	**Facilitate collaboration among NIH intramural and NIH extramural epidemiologists.**	Natural History, Epidemiology, and Prevention Research pg. 39	**88 pg. 109**	
B.	**Peer Review**			
B1	**Restructure an existing IRG to create a study section devoted to prevention science research.**	Natural History, Epidemiology, and Prevention Research pg. 39	**89 pg. 110**	**8 pg. 17**
B2	**Increase the interaction between prevention science NIH extramural program staff and existing IRGs so that program research priorities are understood more fully.**	Natural History, Epidemiology, and Prevention Research pg. 39	**90 pg. 110**	**2-6, 131, 132, 335, 340, 352 pgs. 13-15, 142, 143, 285, 288, 295**
B3	**Consider alternatives to the usual designation of a primary and secondary reviewer when a project is highly multidisciplinary.**	Natural History, Epidemiology, and Prevention Research pg. 39	**91 pg. 110**	
B4	**Improve mechanisms for peer review of research proposals funded by master contracts, such as the HIVNET.**	Natural History, Epidemiology, and Prevention Research pg. 39	**92 pg. 111**	
C. **C1**	**Cross-Institute and Interagency Collaborations** **Commit to expanding and strengthening collaboration among ICDs within the NIH and among other Federal agencies.**	Natural History, Epidemiology, and Prevention Research pg. 40	**93 pg. 111**	
D. **D1**	**Cross-Disciplinary Research: Overlap With Other Panels** **Extend the collaboration developed within the framework of the Area Review Panels to include the activities of the five OAR Coordinating Committees.**	Natural History, Epidemiology, and Prevention Research pg. 40	**94 pg. 112**	
E. **E1**	**Links Among Research, Services, and Communities** **Extend the CAB models developed for clinical trial networks and cohort studies to include community involvement in the area of prevention science research.**	Natural History, Epidemiology, and Prevention Research pg. 41	**95 pg. 113**	
F. **F1**	**Links Between the Public and Private Sectors** **Proactively collaborate with private donors and other sources of venture capital to stimulate biotechnical development.**	Natural History, Epidemiology, and Prevention Research pg. 42	**96 pg. 114**	**31 pg. 45**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
F2 **While exploring the AIDS research opportunities offered by private organizations, NIH should critically evaluate the efficiency and scientific productivity of master contract mechanisms.**	Natural History, Epidemiology, and Prevention Research pg. 42	**97 pg. 114**	
G. **Access and Ownership of the Products of NIH-Supported AIDS Research** **G1** **Streamline and coordinate mechanisms for access to existing repositories of data and biomedical specimens, while emphasizing the need for qualified scientists not funded by the primary research network to work closely with epidemiologists and other scientists working within the research network.**	Natural History, Epidemiology, and Prevention Research pg. 43	**98 pg. 115**	**42 pg. 57**
BEHAVIORAL, SOCIAL SCIENCE, AND PREVENTION RESEARCH AREA REVIEW PANEL	**Behavioral, Social Science, and Prevention Research**		
1. **Support for Behavioral, Social Science, and Prevention Research should be increased substantially to at least double its current level. This, in turn, should be allocated according to the scientific priorities identified in the annual update of the NIH Plan for HIV-Related Research.**	Behavioral, Social Science, and Prevention Research pg. 8	**99 pg. 119**	
2. **The Panel recommends that the OAR take a leadership role, using its Coordinating Committee mechanism, to ensure that the scientific priorities identified for AIDS-related behavioral and social science research at the NIH are responsive to the recommendations of this report, and that as newly emerging issues are identified, research is initiated to address them. The Coordinating Committee should include external (non-NIH) members and be used to stimulate trans-ICD and trans-disciplinary activities. Examples of such activities include developing joint Request for Applications (RFAs), establishing lead agencies for specific priorities, and establishing coordination with other PHS agencies (e.g., CDC, Substance Abuse and Mental Health Services Administration [SAMHSA], Health Resources and Services Administration [HRSA]).**	Behavioral, Social Science, and Prevention Research pg. 8	**100 pg. 119**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
3. The NIH, with collaboration from CDC, should establish sentinel stations in key areas throughout the United States that have different levels of seroprevalence. This can have multiple benefits, such as providing the ability to (1) monitor changes in risk behaviors, (2) identify new risk groups, (3) evaluate both naturally occurring and planned intervention efforts in a timely manner, and (4) conduct pilot intervention research for later development of R01s. (An underutilized mechanism, the P-30 Center grant, may be suitable for providing funds for this type of multisite undertaking.)	Behavioral, Social Science, and Prevention Research pg. 9	**101 pg. 120**	
4. The OAR should develop guidelines, criteria, and a process for rating the AIDS-relevance of projects funded with NIH AIDS dollars. To implement this coding scheme, the principal investigator on a proposal should be required to prepare a brief rationale justifying the AIDS-relevance of the project if AIDS funds are expected to be used to support the project. The study section would be charged with determining whether the project met the criteria specified by the OAR.	Behavioral, Social Science, and Prevention Research pg. 10	**102 pg. 121**	**44-46 pgs. 65, 66**
5. The OAR should stimulate coordination among the NIH and other PHS agencies responsible for primary prevention and early intervention in HIV. This process should establish mechanisms for assessing, on a regular basis, the concerns of front-line HIV providers and integrating these concerns into the NIH research agenda.	Behavioral, Social Science, and Prevention Research pg. 11	**103 pg. 122**	
6. The Panel recommends ongoing and increased NIH support for international efforts in Behavioral, Social Science, and Prevention Research through the spectrum of funding mechanisms used by the ICDs.	Behavioral, Social Science, and Prevention Research pg. 11	**104 pg. 123**	
7. NIDA should support research that recognizes the diversity among the drug-using population (and their social networks) vulnerable to HIV. Relevant groups include homeless youth (the majority of whom are drug users), gay and bisexual drug users (especially IDUs), women at risk either through their own drug use or through sexual activity with drug users, including women who trade sex for money or drugs, and IDUs and crack smokers in the criminal justice system.	Behavioral, Social Science, and Prevention Research pg. 14	**105 pg. 125**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
8. NIMH should expand its prevention research to additional populations including young and ethnic minority MSM, heterosexual minority and poor men, and young people in situations that make them vulnerable to HIV risk behavior.	Behavioral, Social Science, and Prevention Research pg. 14	**106 pg. 126**	
9. The NIH should support more research that assesses the social, environmental, and cultural factors influencing changes in risk behaviors. Cross-national studies may be particularly useful for conducting research with units of analysis larger than the individual.	Behavioral, Social Science, and Prevention Research pg. 15	**107 pg. 128**	**53, 115 pgs. 73, 132**
10. In addition to studies of the sociocultural influences on risk behaviors, the NIH should encourage research that permits the identification of specific elements of successful interventions that may be related to behavior change (e.g., outreach, counseling, skills training, peer influences, or other components).	Behavioral, Social Science, and Prevention Research pg. 15	**108 pg. 128**	
11. The NIH should encourage and support the use of quasi-experimental design alternatives (to the randomized controlled trial) that permit community-level trials to be undertaken in field-demonstration studies.	Behavioral, Social Science, and Prevention Research pg. 17	**109 pg. 129**	**75 pg. 89**
12. The NIH should encourage and support studies that assess the cost-effectiveness and cost-utility of behavior change interventions, including those that estimate or measure the number of potential HIV infections averted by an intervention.	Behavioral, Social Science, and Prevention Research pg. 17	**110 pg. 129**	
13. Basic research supported by NIMH, NICHD, and NIDA should be conducted within the following high-risk, understudied groups: gay men of color, young gay men, women who have sex with IDUs, bisexual men, and gay and bisexual drug users.	Behavioral, Social Science, and Prevention Research pg. 19	**111 pg. 130**	
14. The following groups, currently with lower HIV prevalence, also merit special study because of their potential vulnerability: persons who are mentally ill, incarcerated persons, young adolescents (under 15 years of age), and later middle age and older adults. Research involving these groups should be supported by NIMH, NICHD, NIDA, and NIA, as appropriate.	Behavioral, Social Science, and Prevention Research pg. 19	**112 pg. 130**	**111 pg. 130**
15. NIDA, NIMH, NICHD, and NIAAA should support theory-building studies that are specifically developed in the context of HIV prevention research, in contrast to studies that simply apply or adapt theories from other domains.	Behavioral, Social Science, and Prevention Research pg. 20	**113 pg. 131**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
16. NIDA, NIMH, NIAAA, and NICHD should support qualitative/descriptive/ethnographic studies of the subjective difficulties individuals experience in their attempts to practice safer sex or safer drug-using behavior, and of situations/contexts that are subjectively experienced as difficult for enacting and maintaining safer behavior.	Behavioral, Social Science, and Prevention Research pg. 20	**114 pg. 131**	**113 pg. 131**
17. All ICDs with a behavioral and social science portfolio should support basic research that involves units of analyses other than the individual.	Behavioral, Social Science, and Prevention Research pg. 20	**115 pg. 132**	**53, 107 pgs. 73, 128**
18. NICHD and NIMH, individually or collaboratively, should support basic research on those individual differences in human sexuality—cultural, cognitive, affective, and neurophysiological—that impact the sexual transmission of HIV. For example, attention should be paid to the relevance of the relationship (i.e., intimate/romantic, involving strong emotional bonds) on sexual risk behavior, and also to neurobiological mechanisms that might interfere with sexual self-regulation in the context of safer sex practices.	Behavioral, Social Science, and Prevention Research pg. 21	**116 pg. 133**	
19. NIAAA, NIMH, and NIDA should support studies that examine in detail the use and abuse of alcohol/drugs within the context of sexual encounters and the direct effects of these intoxicants on sexual self-regulatory mechanisms.	Behavioral, Social Science, and Prevention Research pg. 22	**117 pg. 134**	
20. NIDA and NIAAA should devote special attention to research on the impact of drug and alcohol use on the sexual transmission of HIV among gay men and on how initiation into alcohol and/or drug use might have an impact on sexual risk taking among adolescents.	Behavioral, Social Science, and Prevention Research pg. 22	**118 pg. 134**	
21. NIDA should expand its support for studies on the exchange of drugs for sex and sex for drugs to include substances other than crack cocaine.	Behavioral, Social Science, and Prevention Research pg. 22	**119 pg. 135**	
22. NICHD and NIMH should support research on the sexual transitions of young adolescents including research on the initiation into homosexual and/or heterosexual activity and the related "coming out" or "experimenting" processes. In addition, studies are needed that investigate the biological and social precursors of these transitions, particularly when they are not voluntary.	Behavioral, Social Science, and Prevention Research pg. 23	**120 pg. 136**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
23. NIDA and NICHD should support research on the progression of substance use over time. Recent findings suggest that first-time initiates and younger drug users are turning to forms of noninjection drug use in part to avoid HIV transmission. Studies are needed that investigate and map possible progressions into riskier forms of drug use in relation to HIV transmission.	Behavioral, Social Science, and Prevention Research pg. 23	**121 pg. 137**	
24. NIA should collaborate with NIMH and NICHD to support more descriptive research about the HIV risk behavior of individuals who are in life stages and/or transitions that increase risk. These groups include pregnant unmarried women, recently divorced men and women, and individuals over the age of 50.	Behavioral, Social Science, and Prevention Research pg. 23	**122 pg. 137**	**120 pg. 136**
25. NIMH, NICHD, and NIDA should support research on "resilient" individuals who, in the face of difficult circumstances, are successful in adopting and maintaining safe sex and/or drug-using behavior.	Behavioral, Social Science, and Prevention Research pg. 24	**123 pg. 137**	
26. NIMH and NICHD should support research on the relationship between "sexual addiction" and HIV risk taking.	Behavioral, Social Science, and Prevention Research pg. 24	**124 pg. 138**	
27. Intervention studies funded by NIH should analyze systematically the reasons, variables, and/or characteristics that may explain individuals' susceptibility (or resistance) to HIV interventions.	Behavioral, Social Science, and Prevention Research pg. 24	**125 pg. 139**	**123 pg. 137**
28. NIMH, NICHD, and NIDA should support longitudinal studies of individuals' and/or groups' ability to maintain safe behavior over time and of those factors that may inhibit or promote relapse to unsafe practices.	Behavioral, Social Science, and Prevention Research pg. 25	**126 pg. 139**	**124 pg. 138**
29. NIMH and NIDA should support (in some cases in collaboration with other ICDs) research to prevent transmission by HIV-infected persons, including studies to determine the prevalence and determinants of risk behavior among HIV-infected persons and studies to develop and test interventions to reduce behaviors that place others at risk.	Behavioral, Social Science, and Prevention Research pg. 26	**127 pg. 139**	
30. NIMH, NIDA, NICHD, NIA, and NINR (as relevant) should increase intervention research directed toward improving coping and quality of life among HIV-infected persons from all populations, across the full time-course of HIV illness.	Behavioral, Social Science, and Prevention Research pg. 28	**128 pg. 140**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
31. NIMH and NIDA should expand research describing the impact of HIV disease on formal and informal caregivers, as well as on family members, and they should increase intervention research designed to address the needs of these groups.	Behavioral, Social Science, and Prevention Research pg. 29	**129 pg. 141**	
32. NIMH and NIDA should initiate research on the impact of stigmatization on HIV-infected persons, including the influence of stigmatization on coping with HIV disease, decisions regarding treatment, and quality of life.	Behavioral, Social Science, and Prevention Research pg. 29	**130 pg. 142**	
33. Conduct coordinated and collaborative research on the pathobiology of nervous system HIV infection and nervous system injury underlying the AIDS dementia complex, peripheral neuropathies, and other CNS and PNS complications of HIV and AIDS. These studies should be multidisciplinary efforts that focus on the cellular and molecular basis of viral latency, gene expression and replication in neural tissue, and the regional, cellular, neurochemical, and molecular basis of neural dysfunction. Research strategies should involve direct studies of human infection, animal models (including a spectrum of lentivirus models), and cell culture studies. NINDS, NIMH, NIDA, NIAID, and NICHD should work together to ensure that these studies benefit from broad expertise, state-of-the-art science, and the efficient utilization of resources.	Behavioral, Social Science, and Prevention Research pg. 31	**131 pg. 142**	
34. Expand research on the treatment of the neurological and psychiatric sequelae of HIV infection. The scope of this research should range from cell culture and animal models to human clinical trials. These efforts should also involve cooperation and coordination among NINDS, NIMH, NIAID, NICHD, and other ICDs as appropriate.	Behavioral, Social Science, and Prevention Research pg. 31	**132 pg. 143**	**131 pg. 142**
35. Initiate research to investigate the determinants and barriers to timely HIV testing and entrance into care by HIV-infected persons from all vulnerable populations.	Behavioral, Social Science, and Prevention Research pg. 32	**133 pg. 143**	
36. Develop and test intervention strategies to increase the early identification, timely entrance into care, and effective management of disease in HIV-infected persons from all vulnerable populations.	Behavioral, Social Science, and Prevention Research pg. 32	**134 pg. 143**	**133 pg. 143**
37. NIMH, NIAID, and, where appropriate, NIDA should cooperate to support research to determine the social, psychological, environmental, and medical factors associated with recruitment, adherence, and retention in clinical trials and care for persons with HIV/AIDS.	Behavioral, Social Science, and Prevention Research pg. 33	**135 pg. 144**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
38. NIMH, NIAID, and, where appropriate, NIDA should cooperate to support research to develop and test intervention strategies to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV-infected persons from all vulnerable populations.	Behavioral, Social Science, and Prevention Research pg. 34	**136 pg. 144**	**135 pg. 144**
39. Because methodological issues transcend specific ICDs, the OAR should establish committees of experts and support them on an ongoing basis to develop standards regarding the use of various design options and guidelines for the appropriate use of various outcome measures (e.g., self-reported behavior, incident STDs, or HIV).	Behavioral, Social Science, and Prevention Research pg. 36	**137 pg. 146**	
40. The ICDs should develop programs, using the RFA or contract process, to stimulate methodological research on the issues identified in this report or through the ongoing process of scientific priority setting under the direction of the OAR.	Behavioral, Social Science, and Prevention Research pg. 36	**138 pg. 146**	**137 pg. 146**
41. Given the crucial importance of training for the research enterprise, the OAR should appoint a separate coordinating committee to review and make recommendations on NIH AIDS-related activities listed under "Training and Infrastructure" in the NIH Plan for HIV-Related Research.	Behavioral, Social Science, and Prevention Research pg. 39	**139 pg. 148**	**9 pg. 17**
42. The OAR should develop a coordinated plan for HIV/AIDS-specific behavioral science research training that takes advantage of a wider range of NIH training mechanisms (such as the K awards, supplements, and predoctoral research opportunities). The plan should include strategies for the systematic outcome evaluation of training awards.	Behavioral, Social Science, and Prevention Research pg. 39	**140 pg. 148**	**9-13 pgs. 17-22**
43. The NIH should increase funding and programs for AIDS-related research training explicitly tailored and targeted to ethnic minority individuals, primarily at the postdoctoral level. These programs should involve collaborative mentoring activities in research projects defined by the minority scientists, rather than simply providing supplements to existing grants. Programs should include intense and long-term mentoring and support in the NIH grant application process, and they should be evaluated in relation to a measurable increase in the number of minority NIH-funded principal investigators at the NIH.	Behavioral, Social Science, and Prevention Research pg. 40	**141 pg. 149**	**13 pg. 22**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
44. Priorities developed in this evaluation process should be used to guide the development of new RFAs by the ICDs.	Behavioral, Social Science, and Prevention Research pg. 41	**142 pg. 149**	
45. Study section composition should be informed by scientific priorities identified through this and other OAR processes. Study sections should be briefed regularly by OAR and ICD program staff on the scientific priorities identified through OAR processes.	Behavioral, Social Science, and Prevention Research pg. 41	**143 pg. 149**	**6 pg. 15**
46. Study sections should review grants for the degree to which they meet the scientific priorities established through this and other OAR processes.	Behavioral, Social Science, and Prevention Research pg. 41	**144 pg. 149**	**6 pg. 15**
47. In the next planning cycle, the Behavioral and Social Science Coordinating Committee should define not only priorities but also criteria for determining whether or not grants meet these priorities.	Behavioral, Social Science, and Prevention Research pg. 42	**145 pg. 150**	**44-46 pgs. 65, 66**
48. The NIH should eliminate the "triage" mechanism implemented in the recently revised grant review process.	Behavioral, Social Science, and Prevention Research pg. 42	**146 pg. 150**	
49. The Panel strongly recommends that the OAR, in cooperation with the ICDs and through the coordinating committee process, develop guidelines for coding AIDS research by scientific areas, and that these guidelines be used across future fiscal years to ensure that it will be possible to trust analyses of funding by areas of science and objectives, and to ensure that multiyear analyses will be possible.	Behavioral, Social Science, and Prevention Research pg. 42	**147 pg. 150**	**44-46 pgs. 65, 66**
50. Expedited funding should be made available to projects seeking to evaluate naturally occurring social or legislative changes.	Behavioral, Social Science, and Prevention Research pg. 43	**148 pg. 151**	
51. The OAR should target funds to ICDs for secondary analysis of existing datasets.	Behavioral, Social Science, and Prevention Research pg. 43	**149 pg. 151**	**41 pg. 55**
52. NIDA should reverse the proportions of its treatment research portfolio and its harm reduction portfolio to give greater weight to the latter.	Behavioral, Social Science, and Prevention Research pg. 43	**150 pg. 153**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
53. NIDA should support a "second generation" of studies related to the operations and the impact of needle/syringe-exchange programs on individual participants and communities. The relationship between such programs and other HIV prevention services (including drug treatment) should be particularly encouraged.	Behavioral, Social Science, and Prevention Research pg. 48	**151 pg. 153**	
54. NIMH should allocate its AIDS resources in Behavioral and Social Science Research in better accord with the priorities of the NIH Plan for HIV-Related Research, giving a greater proportion to Primary Prevention/Intervention Research.	Behavioral, Social Science, and Prevention Research pg. 48	**152 pg. 154**	
55. NIMH should support preventive interventions with a broader range of theoretical perspectives from the behavioral and social sciences than currently is present.	Behavioral, Social Science, and Prevention Research pg. 50	**153 pg. 155**	
56. NIMH should expand its strong focus on primary prevention trials to support more community- and social (including legal and policy)-level interventions (rather than small-group risk reduction interventions) and to increase emphasis on the maintenance of behavior change.	Behavioral, Social Science, and Prevention Research pg. 50	**154 pg. 155**	
57. NIMH should encourage multilevel sustained behavior change intervention models that draw upon many different theories and intervention modalities rather than emphasize "pure tests" of single theories. The review process must be sensitive to and reflect recognition of the merits and validity of this approach.	Behavioral, Social Science, and Prevention Research pg. 50	**155 pg. 156**	
58. NIMH should broaden its support of social science research, including studies of social, policy, and legal change related to HIV prevention and cost-effectiveness and cost-benefit analyses of various HIV intervention modalities.	Behavioral, Social Science, and Prevention Research pg. 50	**156 pg. 156**	
59. NIAID should not use HIVNET to conduct social and behavioral intervention research unless or until the appropriate expertise can be integrated into the HIVNET governance and review processes.	Behavioral, Social Science, and Prevention Research pg. 52	**157 pg. 157**	
60. NICHD should support more HIV preventive intervention research focused on youth most vulnerable to HIV infection and should develop mechanisms for disseminating findings from such research to communities and service organizations.	Behavioral, Social Science, and Prevention Research pg. 54	**158 pg. 158**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
61. NIAAA should be commended for its effort to support HIV-related behavioral research with such a small budget. However, a better balance should be struck between pre-intervention and primary prevention/intervention research, requiring that greater resources be devoted to the latter over the next few years.	Behavioral, Social Science, and Prevention Research pg. 55	**159 pg. 161**	
62. NIAAA and other Institutes such as NIDA or NIMH should develop methods to foster greater integration and collaboration on intervention (as well as basic science) research on the relationship between alcohol, other drug use, and HIV transmission risk. These could include (1) joint development and support of RFAs; (2) representatives from other NIH Institutes (such as NIDA or NIMH) participating in program reviews for NIAAA; (3) specific RFPs, jointly sponsored, to encourage intervention research related to alcohol and drug use and HIV transmission risk behaviors and their contexts (particularly with respect to drug injectors and crack cocaine users).	Behavioral, Social Science, and Prevention Research pg. 55	**160 pg. 162**	
63. The Panel recommends that NIA resume its commitment to HIV/AIDS and aging research by issuing its own PA, RFA, or RFP, in addition to participating in those initiated by other ICDs.	Behavioral, Social Science, and Prevention Research pg. 57	**161 pg. 162**	
ETIOLOGY AND PATHOGENESIS AREA REVIEW PANEL	**Etiology and Pathogenesis**		
Cross-Cutting Recommendations from the Executive Summary			
1. Increased emphasis on investigator-initiated research through doubling of the R01 pool of funding.	Etiology and Pathogenesis pg. 1	**162 pg. 167**	**178 pg. 170**
2. Continued, but more selective, use of RFAs with set-aside funding in critical areas of research not addressed by the R01 mechanism; these critical areas should be identified in an ongoing conjoint effort of the ICDs, OAR, scientific advisors, and community representatives.	Etiology and Pathogenesis pg. 1	**163 pg. 167**	**179 pg. 171**
3. Increased support to encourage long-range discovery research and the entry of both new and distinguished established scientists into the field.	Etiology and Pathogenesis pg. 1	**164 pg. 167**	**181 pg. 172**
4. Increased focus on understanding the basic immunology of infected and uninfected human beings and primates and on efforts to attract immunologists to the field.	Etiology and Pathogenesis pg. 1	**165 pg. 167**	**20, 182, 183 pgs. 31, 173**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
5. Redirection of funding away from research projects, both extramural and intramural, that are judged to be of lesser quality or relevance.	Etiology and Pathogenesis pg. 1	**166 pg. 167**	**185 pg. 175**
6. Redirection of funding for research or infrastructure currently designated as AIDS-related but which does not meet the rigorous criteria called for by the Panel.	Etiology and Pathogenesis pg. 1	**167 pg. 168**	**186 pg. 175**
7. Open competition and expert peer review to increase access to funding at Regional Primate Research Centers (RPRCs) and the neuro-AIDS centers for training and research.	Etiology and Pathogenesis pg. 1	**168 pg. 168**	**37-39 pgs. 51-53**
8. Restoration of resources to the most relevant nonhuman primate model.	Etiology and Pathogenesis pg. 1	**169 pg. 168**	**200 pg. 183**
9. Greater involvement of the extramural scientific community in the design of natural history studies to engender hypothesis-driven collection of specimens.	Etiology and Pathogenesis pg. 1	**170 pg. 168**	**42 pg. 57**
10. Separation of collection of specimens from access to specimens by all qualified investigators.	Etiology and Pathogenesis pg. 1	**171 pg. 168**	**42 pg. 57**
11. Open competition and comparable criteria for funding for all mechanisms and programs.	Etiology and Pathogenesis pg. 2	**172 pg. 169**	**189 pg. 178**
12. Improved peer review, from the composition of the study sections to shared oversight by the ICDs and OAR.	Etiology and Pathogenesis pg. 2	**173 pg. 169**	**192 pg. 179**
13. Improved management and AIDS focus achieved by: **• Fully vesting OAR with the fiscal and scientific authority to coordinate the total NIH AIDS effort, intramural and extramural, but operating by regularly and systematically soliciting advice from leading scientists and community representatives in the formulation and evaluation of its plans for pathogenesis research;**	Etiology and Pathogenesis pg. 2	**174 pg. 169**	**187 pg. 176**
• Restructuring the AIDS information retrieval system; and	Etiology and Pathogenesis pg. 2	**175 pg. 169**	**43 pg. 62**
• Devising a mechanism to define AIDS-related research (ARR) that is both rigorous and evolving in response to new scientific priorities.	Etiology and Pathogenesis pg. 2	**176 pg. 169**	**44 pg. 65**
Recommendations from the Report			

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
1.	**Improve the scientific portfolio: programs and human and fiscal resources.**	Etiology and Pathogenesis pg. 4	**177 pg. 170**	**179, 181 pgs. 171, 172**
1a.	**Double the support for unsolicited investigator-initiated AIDS research (even if this results in different paylines for AIDS and non-AIDS research).**	Etiology and Pathogenesis pg. 5	**178 pg. 170**	
1b.	**Use RFAs with set-aside funding selectively, both to focus attention on important areas of pathogenesis research and to bring established or new high-caliber scientists into the field.**	Etiology and Pathogenesis pg. 5	**179 pg. 171**	
2.	**Enhance the emphasis on long-range discovery research in areas of highest priority, especially human immunology.**	Etiology and Pathogenesis pg. 6	**180 pg. 172**	
2a.	**Use Merit and similar awards (e.g., The Javits Award) and create incentives to encourage long-range and innovative research.**	Etiology and Pathogenesis pg. 6	**181 pg. 172**	**180 pg. 172**
2b.	**Convene a series of meetings of expert non-AIDS and HIV/SIV immunologists to consider ways of engaging immunologists in the effort to address the critical issues and to overcome the challenges of studying the immune systems of genetically complex humans and nonhuman primates.**	Etiology and Pathogenesis pg. 6	**182 pg. 173**	
2c.	**Provide supplemental funding to attract immunologists into the field.**	Etiology and Pathogenesis pg. 6	**183 pg. 173**	**11-13 pgs. 18-22**
2d.	**Establish consortial approaches between basic immunologists and investigators currently engaged in AIDS research. The anticipated benefits of the consortial mechanisms include overcoming basic immunologists' unfamiliarity with AIDS research and concerns about working with infectious agents; facilitating exchange of ideas, techniques, reagents, and personnel; and increasing the likelihood that postdoctoral fellows will go into AIDS research.**	Etiology and Pathogenesis pg. 6	**184 pg. 174**	**20 pg. 31**
2e.	**Funds from these programs of poor quality, productivity, and relevance should be redirected.**	Etiology and Pathogenesis pg. 7	**185 pg. 175**	
2f.	**Rigorous guidelines on what constitutes AIDS and ARR will likely free up needed resources.**	Etiology and Pathogenesis pg. 7	**186 pg. 175**	

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
2g.	**OAR should establish mechanisms involving the extramural scientific community, such as the annual scientific planning workshops, for open discussion and decision on the portion of the AIDS research budget that would be appropriate to use to support the general costs of biomedical research (matched by services received) and of AIDS research that are nominally designated currently as etiology and pathogenesis.**	Etiology and Pathogenesis pg. 7	**187 pg. 176**	**44 pg. 65**
3.	**Improve peer review, quality control, and AIDS focus.**	Etiology and Pathogenesis pg. 7	**188 pg. 177**	**2 pg. 13**
3a.	**Open competition for funding from all sources: grants, contracts, cooperative agreements, and centers should take place.**	Etiology and Pathogenesis pg. 7	**189 pg. 178**	
3b.	**OAR should apply comparable NIH-wide criteria in evaluations of intramural and extramural research by the quality of science and the qualifications and productivity of the scientists and by the focus and potential impact on AIDS.**	Etiology and Pathogenesis pg. 7	**190 pg. 178**	
3c.	**These evaluations should be recurring regular reviews of all programs (extramural and intramural) with NIH funding by reviewing bodies with a majority of non-Government scientists.**	Etiology and Pathogenesis pg. 7	**191 pg. 178**	**190 pg. 178**
3d.	**Peer review should be improved.**	Etiology and Pathogenesis pg. 7	**192 pg. 179**	
3e.	**The research focus on AIDS should be improved.**	Etiology and Pathogenesis pg. 8	**193 pg. 180**	**2, 6 pgs. 13, 15**
•	**The Panel endorses changes in DRG recommended in the Cassman Report, which call for a peer-review oversight group (PROG) and peer review conducted by both DRG and ICDs, as appropriate. A body similar to PROG should be established for intramural research.**	Etiology and Pathogenesis pg. 8	**194 pg. 181**	**190 pg. 178**
•	**OAR should have separate and parallel input to the final evaluation and ranking of review panels. For grants that remain classified as AIDS/AIDS-related following council review, funding decisions should be made by the Institute Director in consultation with the Director of OAR.**	Etiology and Pathogenesis pg. 8	**195 pg. 182**	**2, 6 pgs. 13, 15**
4.	**Formulate and implement mechanisms to increase access to and improve the use of critical resources such as RPRCs and central repositories.**	Etiology and Pathogenesis pg. 8	**196 pg. 182**	**36, 37, 39, 42 pgs. 50, 51, 53, 57**

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
4a.	**Competition for AIDS research project funding by NCRR at RPRCs should be opened to all extramural investigators, rather than only to permanent Center staff.**	Etiology and Pathogenesis pg. 8	**197 pg. 182**	**36, 37 pgs 50, 51**
4b.	**The NCRR study sections that review the RPRCs should incorporate expertise in AIDS and ARR.**	Etiology and Pathogenesis pg. 8	**198 pg. 183**	**38 pg. 52**
4c.	**There should also be open competition for all relevant animal cost-funding of DRG-reviewed grants through a regularly recurring RFA.**	Etiology and Pathogenesis pg. 8	**199 pg. 183**	**39 pg. 53**
4d.	**In view of the limited utility of chimpanzees for studies of AIDS pathogenesis, resources currently set aside for breeding and maintaining chimpanzees would be better used by NCRR for openly competed studies in macaques.**	Etiology and Pathogenesis pg. 9	**200 pg. 183**	
4e.	**OAR, in conjunction with the ICDs and extramural scientific community, should establish NIH-wide guidelines for access to clinical samples.**	Etiology and Pathogenesis pg. 9	**201 pg. 184**	**42 pg. 57**
5.	**Define and focus the scientific portfolio of AIDS and AIDS-related research and associated program resources.**	Etiology and Pathogenesis pg. 9	**202 pg. 184**	**44 pg. 65**
5a.	**The NIH and OAR should develop a new AIDS information system that lists grant titles and numbers, investigators' names and institutions, dollar amounts, funding ICDs, and abstracts; is searchable by these parameters and by topic area (e.g., MESH headings); lists publications stemming from the research; can be applied equally to all NIH-funded AIDS research, both intramural and extramural; and is user-friendly and accessible to all those involved in the evaluation of NIH-funded AIDS research.**	Etiology and Pathogenesis pg. 9	**203 pg. 184**	**43 pg. 62**
5b.	**Establish an evolving mechanism to define ARR through a conjoint effort of the ICDs and OAR, with involvement of the extramural research community. This definition should be broad but rigorous, consistent across ICDs, and updated annually. An explicit defensible rationale to define ARR should be linked to scientific issues and strategies and should be redefined as scientific progress reveals new areas of relevance. Research proposals should be predesignated by the principal investigator (PI) as AIDS or ARR and reviewed by appropriate panels that include OAR staff.**	Etiology and Pathogenesis pg. 10	**204 pg. 185**	**44 pg. 65**
6.	**Maintain a strong OAR.**	Etiology and Pathogenesis pg. 10	**205 pg. 185**	

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
6a.	**OAR should set the scientific agenda and priorities in a collaborative effort with the directors of the ICDs, coordinating committees, working groups, councils and advisory bodies, non-Government researchers, and community representatives. To better communicate scientific priorities and funding, relevant study section chairs should be included in the process of setting the scientific agenda.**	Etiology and Pathogenesis pg. 10	**206 pg. 185**	**2 pg. 13**
6b.	**OAR should align programs and resources by having and exercising fiduciary control over all NIH AIDS programs (not only the control over new and competing funds that were assigned to OAR in the NIH Revitalization Act of 1993), including intramural research, contracts, and cooperative agreements. Without central fiscal authority to fund scientific priorities, the identification of these priorities becomes a meaningless exercise.**	Etiology and Pathogenesis pg. 10	**207 pg. 186**	
6c.	**OAR and the ICDs should continue to regularly and systematically solicit advice from leading Government and non-Government scientists in the formulation and plans for pathogenesis research.**	Etiology and Pathogenesis pg. 11	**208 pg. 186**	**44, 124 pgs. 65, 138**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
ANIMAL MODEL SUBPANEL REPORT OF THE ETIOLOGY AND PATHOGENESIS PANEL REPORT	**Etiology and Pathogenesis**		
With a certainty that animal models will continue to be important in the future for studying AIDS pathogenesis, continued support for animal model research is warranted. A broadly based portfolio that supports research into natural lentiviral infections of many species is encouraged. For focused AIDS-specific questions, emphasis should be placed on nonhuman primate models in which AIDS occurs. Murine systems will be useful for restricted purposes. Funding mechanisms that bypass true, open competition for funds should be eliminated. If an Institute is not in a position to oversee open competition for the funds, these funds should be dispensed to other Institutes.	Etiology and Pathogenesis pg. 33	**209 pg. 186**	**231, 233 pgs. 204, 207**
NEUROPATHOGENESIS SUBPANEL REPORT OF THE ETIOLOGY AND PATHOGENESIS PANEL REPORT	**Etiology and Pathogenesis**		
OAR should coordinate all efforts directed at neuro-AIDS across the NIH in all intramural and extramural programs, and by all mechanisms, to align the research programs with the scientific priorities. The RFA on the blood brain barrier and neuro-AIDS jointly issued by NIMH and NINDS and workshops on neuro-AIDS cosponsored by NIMH, NINDS, and NIAID provide recent and past examples of fruitful cooperative ventures and a paradigm for the future, for both research and training.	Etiology and Pathogenesis pg. 36	**210 pg. 187**	
Substantial support for research the Subpanel views as highly relevant and likely to impact greatly on neuro-AIDS can be generated by redirecting and refocusing resources, using existing mechanisms that involve OAR, the NIH, and non-Government scientific communities. The coordinating committees and annual OAR workshops define and redefine scientific priorities and AIDS related research. These definitions should be utilized to align programs and resources and to replace current practices in that research that is tangentially related to neuro-AIDS or apparently unrelated but important to neuroscience that might eventually prove related (such as work on opiate receptors) is classified as ARR. This work should be supported on its own merits and not as ARR. Similarly, practices of arbitrarily assigning funding as neuro-AIDS, e.g., in ACTUs, should be discontinued in favor of rigorous and explicit rationales for designating funding as neuro-AIDS.	Etiology and Pathogenesis pg. 36	**211 pg. 188**	

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Shared resources are critical to the success of understanding the pathogenesis of neuro-AIDS. These resources include the primate centers, designated centers for neuro-AIDS research, and tissue repositories essential for research with *in vivo* relevance. The Subpanel endorses the conclusions of a number of the Area Review Panels that access to the primate and transgenic murine models must be improved. The Subpanel also supports efforts to improve centralized systems to collect, catalog, and distribute reagents and tissue specimens and the involvement of the scientific community in determining the type and frequency of sample collection.	Etiology and Pathogenesis pg. 37	**212 pg. 189**	**42 pg. 57**
VACCINE RESEARCH & DEVELOPMENT AREA REVIEW PANEL	**Vaccine Research and Development**		
<u>Basic Research</u>			
• **Create an IRG that would be dedicated to broad aspects of vaccine research, including both HIV and other pathogens.**	Vaccine Research and Development pg. 3	**213 pg. 193**	**8 pg. 17**
• **Continue NIH/NIAID efforts to encourage and solicit the research community to submit applications in vaccine biology and immunology.**	Vaccine Research and Development pg. 3	**214 pg. 193**	
• **Selectively target vaccine-related research areas for special consideration during review and funding.**	Vaccine Research and Development pg. 3	**215 pg. 193**	**225 pg. 200**
• **Increase the access of basic research scientists, who are interested in HIV interactions with the human immune system, to clinical materials emerging from studies within existing networks such as the Multicenter AIDS Cohort Study (MACS), the AIDS Vaccine Evaluation Group (AVEG), and the HIV Network for Efficacy Trials (HIVNET) and from certain animal model studies.**	Vaccine Research and Development pg. 3	**216 pg. 194**	**42 pg. 57**
<u>Targeted Research</u>			
• **The Panel specifically supports and commends the recent establishment of a Vaccine Design Focus Group by NIAID. This group is composed of intramural and extramural investigators from both academia and industry who have direct experience in vaccine design and immunogenicity and are empowered to make appropriate priority choices.**	Vaccine Research and Development pg. 3	**217 pg. 194**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **The charge of this group should be expanded to an NIH-wide effort to: (1) understand the early step in viral infection and pathogenesis in the host, (2) evaluate candidate vaccines in a systematic manner that will allow promising approaches to be identified, (3) determine correlates of immunity, and (4) establish primary (prevention of infection) and secondary (attenuation of infection such that disease is prevented and transmission is curtailed) vaccine goals. Another critical role of the expanded Vaccine Design Focus Group should be to seek out and evaluate new vaccine candidates, so that it can recommend the most promising concepts for clinical testing by the AIDS Vaccine Evaluation Group (AVEG) (see below).**	Vaccine Research and Development pg. 4	**218 pg. 194**	**217 pg. 194**
Clinical Trials			
• **AVEG should work closely with the Vaccine Design Focus Group to encourage the preclinical development of promising vaccine candidates that are suitable for clinical evaluation in Phase I and II studies as well as those that might prove worthy of evaluation for efficacy.** **Guidelines should be established for the advancement of a vaccine product to efficacy trials sponsored by the NIH. Although the precise criteria might vary with the nature of the concept under evaluation, a product ideally should be shown to induce humoral and cellular immunity that is broad, durable, and likely to provide a significant barrier to natural HIV infection. If and when appropriate animal models become available, demonstration of protection in the preclinical evaluation with such models should support the entry of a vaccine into efficacy trials.**	Vaccine Research and Development pg. 4	**219 pg. 195**	**218 pg. 194**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **AVEG also should invest more effort on in-depth comprehensive assessments of human immune responses to HIV antigens. Greater emphasis should be placed on the laboratory analysis of immune responses in vaccinees, even if this necessitates the study of many fewer individuals with any one vaccine candidate. Among immune system parameters that should be evaluated in more detail are the generation, function, and specificity of cytotoxic T lymphocytes (CTLs); the relevance of neutralizing and nonneutralizing antibodies; the importance of Th1 and Th2 subsets of helper T cells; the targeting of immune cells to mucosal sites; the sensitivity to infection and function of antigen-presenting cells (particularly dendritic cells); and the roles of Type 1 versus Type 2 cytokines in specific and nonspecific immunity to viral infection. The participation of non-AVEG investigators in such studies is essential and should be encouraged.**	Vaccine Research and Development pg. 5	**220 pg. 195**	
• **NIAID should rapidly reassess the status of the HIVNET program. It is likely that few expanded (Phase II or efficacy) vaccine trials will be conducted within the next 5 years; thus, a careful reevaluation of the size and nature of HIVNET programs is now needed. The seronegative cohorts that have been established for determination of seroincidence can and should be used to evaluate biomedical and/or behavioral strategies designed for reduction in HIV transmission, as has been proposed by HIVNET. If appropriately sampled, these and future cohorts also would be of value for studies of primary HIV infection and pathogenesis, and studies of early treatment of acute infection. However, because the principal mission of HIVNET has been vaccine preparedness, it is not obvious that HIVNET has the intrinsic expertise or infrastructure to move effectively beyond its original mission. This raises the question of where and how such expanded studies are best undertaken. NIAID should promptly compile a comprehensive research plan for the HIVNET effort that addresses these issues. This plan should be reviewed by a panel of experts in behavioral, epidemiologic, prevention, and pathogenesis research. The Panel also urges NIAID to prepare an overall funding strategy for HIVNET that is congruent with plans for vaccine development, and that should be reviewed by the OAR. Finally, NIAID should strengthen the ties between AVEG and HIVNET so that each group can benefit from the expertise of the other.**	Vaccine Research and Development pg. 5	**221 pg. 196**	**260 pg. 226**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **The Panel found NIAID's extramural vaccine efforts to be well-integrated; however, the vaccine-related activities at the NCI, NIDR, and the NCRR appear to be critically lacking in oversight and coordination. The entire HIV vaccine effort of NIH would best be coordinated by the OAR with centralization in a single ICD, such as NIAID, and with appropriate linkages to other ICDs. Establishment of such a program requires that a strong, effective, and visible leadership structure be created that includes non-Government experts who have had extensive experience in vaccine research and development. Such an organizational structure will also enable OAR to address the problems related to a balanced allocation of annual resources (and discretionary resources) where they are most needed for AIDS Vaccine Research and Development.**	Vaccine Research and Development pg. 6	**222 pg. 198**	**15 pg. 25**
Basic Research Subpanel Report **E. Other Conclusions and Recommendations**			
• **NIH should increase total funds allocated to basic research in support of vaccine design and development. In particular, basic research on immune responses in humans and macaques should be targeted as an area of the highest priority.**	Vaccine Research and Development, pg. 22	**223 pg. 199**	
• **The Division of Research Grants (DRG) should develop a newly configured separate study section for vaccine-related research.**	Vaccine Research and Development pg. 22	**224 pg. 199**	**8 pg. 17**
• **NIH should allocate specific funding for vaccine-related research to stimulate the fundamental research needed in immunology and vaccine design.**	Vaccine Research and Development pg. 22	**225 pg. 200**	
• **All future research devoted to the development and analysis of vaccination strategies should involve forging more extensive collaborative links with cellular immunologists.**	Vaccine Research and Development pg. 23	**226 pg. 201**	
• **Clinical samples, from vaccine trials and relevant NIH-supported natural history cohorts, as well as viral stocks for experimental animal models, should be made more readily available to researchers, with appropriate research plans, outside the groups involved with the initial sample and data acquisition.**	Vaccine Research and Development pg. 23	**227 pg. 202**	**42 pg. 57**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **Approval of these plans should fall within the purview of an independent committee, and not, as at present, solely under the control of the group which has collected the samples. The supply of materials available, and competing demands upon them, should be taken into account. The Panel noted the success of the NIAID AIDS Reference and Reagent Program in providing virus stocks and other reagents obtained from clinical sites and basic researchers for distribution to the research community.**	Vaccine Research and Development pg. 23	**228 pg. 202**	**42, 289 pgs. 57, 251**
• **NIH should reevaluate the relative distribution of resources between clinical evaluation of current vaccine candidates and the development of new ones with potentially greater promise. Redundant funding for clinical trials of similar vaccine candidates should be eliminated in favor of new vaccine concepts. NIH should establish mechanisms for identifying novel approaches to vaccine development and rapidly testing their feasibility.**	Vaccine Research and Development pg. 23	**229 pg. 203**	
• **NIAID and NCI research programs on HIV-1 genetic variation should be better coordinated, both within the NIH and with other agencies pursuing this problem, including the DoD, CDC, EEC, and WHO.**	Vaccine Research and Development pg. 23	**230 pg. 204**	**17 pg. 27**
• **A rationalization of the simian animal model field and a redistribution of funding for a significant fraction of the current animal models is imperative. The Subpanel recommends performance of fewer, but more detailed, studies, each using an increased number of animals.**	Vaccine Research and Development pg. 24	**231 pg. 204**	
• **NIH-supported basic vaccine research on the HIV-1/Chimpanzee model should focus almost exclusively on the development of a challenge strain that would replicate to high titers in these animals and cause disease.**	Vaccine Research and Development pg. 24	**232 pg. 206**	
• **NIH should continue to encourage the use of small animal models (such as cats and mice) for the development and assessment of vaccine concepts.**	Vaccine Research and Development pg. 24	**233 pg. 207**	
Recommendations on Administrative Issues			
• **NCI and NIAID should reevaluate their code assignment procedures to ensure that a more accurate representation of what basic and preclinical research is devoted to the NIH vaccine program.**	Vaccine Research and Development pg. 25	**234 pg. 208**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **NIH should place a very high priority on the creation of a new study section dedicated to fundamental vaccine research topics, either *de novo* or from existing AIDS-related study sections.**	Vaccine Research and Development pg. 25	**235 pg. 209**	**8 pg. 17**
• **Both NIAID and NCI should minimize the amount of funds allocated by Program Staff without outside peer review from contractual or other resources available within these Institutes.**	Vaccine Research and Development pg. 25	**236 pg. 209**	
NIAID • **A relatively small sum of seed money (perhaps derived from the OAR Director's Discretionary Funds) could be placed under the control of an expert peer-review group, specifically to allow vaccine concepts to be evaluated in primates before submission of a more formal research proposal.**	Vaccine Research and Development pg. 25	**237 pg. 210**	
• **Basic research activities should not be supported under the existing contract mechanisms.**	Vaccine Research and Development pg. 26	**238 pg. 211**	
• **The Panel urges Review Committees and Program Staff to recognize the clear need for more support for investigator-initiated research in both basic and applied studies in human and nonhuman primates and encourage approval of the necessary support in appropriate circumstances.**	Vaccine Research and Development pg. 26	**239 pg. 212**	
• **The U01 and U19 mechanism used to support the NCVDGs for conducting multidisciplinary studies of potential AIDS vaccines merits increased support, whereas the interactive R01 mechanism for multidisciplinary studies should be abolished.**	Vaccine Research and Development pg. 26	**240 pg. 213**	
• **To enhance the functioning of both the vaccine development oversight group proposed above (discussed further in the Targeted Vaccine Research Subpanel report) and the efforts of extramural investigators, NIAID should establish and monitor a comprehensive computer database for recording and analyzing information derived from vaccine trials in animals and humans.**	Vaccine Research and Development pg. 26	**241 pg. 213**	
• **The need for an RFA should be reviewed by an expert group comprised of both extramural non-Government scientists and DAIDS Program Staff.**	Vaccine Research and Development pg. 27	**242 pg. 214**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
NCI • **NCI should immediately conduct a rigorous review of all components of its intramural program presently designated as contributing to AIDS vaccine research and development and use this review to determine which of its current vaccine-related programs should be preserved, and at what level of support.**	Vaccine Research and Development pg. 27	**243** **pg. 215**	
• **The Subpanel proposed that AIDS vaccine research activities of the NIH might best be served if the most relevant and competitive intramural programs at the NCI were placed within a single Division, with administrative control by the OAR, with the view of assimilation into the NIAID intramural program.**	Vaccine Research and Development pg. 27	**244** **pg. 215**	
II. Targeted Research Subpanel Report for the Vaccine Panel **B. Recommendations**			
1. NIH should institute a mechanism for accomplishing targeted vaccine research.	Vaccine Research and Development pg. 32	**245** **pg. 217**	
2. NIH should establish a team of extramural-intramural experts for centralized direction of HIV/AIDS targeted vaccine research.	Vaccine Research and Development pg. 33	**246** **pg. 218**	**15, 231** **pgs. 25, 204**
3. The NIH should provide additional funds for targeted vaccine development.	Vaccine Research and Development pg. 34	**247** **pg. 218**	
4. Importance of establishing new funds for a new area of NIH activity.	Vaccine Research and Development pg. 34	**248** **pg. 219**	
III. Clinical Trials Research Subpanel of the Vaccine Panel Key Recommendations for HIV/AIDS Vaccine Clinical Trials Research			
The poor economic prospects for vaccine development appear to be a restraining force on the entire vaccine development effort. OAR, as a high priority, should invest resources in analyzing and proposing solutions to this problem. It may need to attract more industrial-sector participation or consider cooperative or public ownership arrangments for AIDS vaccine products, especially for riskier approaches.	Vaccine Research and Development pg. 48	**249** **pg. 220**	
It is essential that AVEG and DAIDS Program Staff establish a mechanism to allow scientists to request collaboration with contracted programs for studies with clinical samples, with some funds set aside to support such collaborations.	Vaccine Research and Development pg. 49	**250** **pg. 220**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
Criteria for advancement of candidate HIV vaccines should be determined in advance. The decision-making process must be open (i.e., including participation of both the larger scientific and affected community), more clearly defined, and with a specific person or group that has final decision-making authority.	Vaccine Research and Development pg. 49	**251 pg. 221**	
Therefore, new Phase I and Phase II trials should continue to be a high priority even if one or more vaccines advance into efficacy trials.	Vaccine Research and Development pg. 49	**252 pg. 222**	**251 pg. 221**
OAR should develop a process to assist with and review the allocation of resources and coding of projects in the AIDS budget.	Vaccine Research and Development pg. 49	**253 pg. 222**	**44 pg. 65**
NIH should retain the commitment to international trials and scientific collaborations, given the global nature of this disease.	Vaccine Research and Development pg. 49	**254 pg. 222**	
Recommendations for Specific ICDs			
Significant resources should be directed toward using clinical trial networks (AVEG and HIVNET cohorts) to advance our overall knowledge of the immune responses to vaccine strategies.	Vaccine Research and Development pg. 50	**255 pg. 223**	
Laboratories linked to the clinical trials effort should focus on automation of routine assays, development and validation of new and better assays, and more comprehensive studies of the human immune responses to vaccination. It is particularly important that methods to quantify cellular responses, especially CTLs, be encouraged.	Vaccine Research and Development pg. 50	**256 pg. 224**	
NIAID should streamline mechanisms for ensuring access to specimens for investigators outside of AVEG/HIVNET and ensuring available funding for specialized studies.	Vaccine Research and Development pg. 50	**257 pg. 225**	**250 pg. 220**
NIAID should be more active in seeking out and assisting in the production of pilot lots of vaccine candidates, if needed, to test new vaccine strategies.	Vaccine Research and Development pg. 50	**258 pg. 225**	
NIAID should dedicate additional personnel or resources to facilitate the trials "start up" process (protocol development, satisfying FDA requirements, filing investigational new drug [IND] applications, making arrangements with manufacturers) to enter candidate vaccines into Phase I/II trials and ensure effective use of the AVEG trials network.	Vaccine Research and Development pg. 50	**259 pg. 225**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
NIAID should establish a rigorous plan and schedule for deciding the future direction of HIVNET as soon as possible. HIVNET, or selected components, should be decreased in scope or eliminated after baseline studies are completed, unless clearly appropriate vaccine or nonvaccine intervention trials are undertaken or anticipated in the near future.	Vaccine Research and Development pg. 50	**260 pg. 226**	**264 pg. 229**
More of HIVNET's resources should be devoted to educating communities that will eventually participate in trials.	Vaccine Research and Development pg. 50	**261 pg. 227**	
HIVNET should participate in expanded Phase II studies of HIV vaccines, especially when such trials involve people at some risk of HIV infection.	Vaccine Research and Development pg. 51	**262 pg. 228**	**252 pg. 222**
Options should be developed to allow individuals to enroll in studies of the clinical benefit of early treatment, especially if the scope of such studies are expanded to include people with documented recent infections who are already antibody positive.	Vaccine Research and Development pg. 51	**263 pg. 228**	
NIAID should exert closer oversight of HIVNET and the Master Contract mechanisms and initiate regular reevaluation of the funding mechanisms and funding level as changes in vaccine development plans occur.	Vaccine Research and Development pg. 51	**264 pg. 229**	
A reasonable percentage of the cost of HIVNET should be coded for clinical vaccine trial preparedness. The rest of the cost must be justified by the strength of the other reserach and coded appropriately under objectives in the annual NIH Plan for HIV-Related Research.	Vaccine Research and Development pg. 51	**265 pg. 230**	
Trials of HIV vaccines in the infants born to HIV-infected mothers should be conducted independently of trials in other high-risk populations, because the risk of infection, even with AZT treatment, still exceeds that in most at-risk adult populations.	Vaccine Research and Development pg. 51	**266 pg. 230**	
NIAID should explore ways that bring AVEG and HIVNET together that build on the strengths of each group and facilitate sharing of knowledge and skills.	Vaccine Research and Development pg. 51	**267 pg. 231**	
NIAID should consider if and how its intramural program can contribute to the clinical vaccine development effort. This effort should be coordinated with the extramural AVEG efforts.	Vaccine Research and Development pg. 51	**268 pg. 231**	
As NCI vaccine concepts reach the stage for testing in clinical trials for safety and immunogenicity, every effort should be made to advance them into existing NIAID Phase I/II trial programs to avoid duplication of resources and effort.	Vaccine Research and Development pg. 51	**269 pg. 232**	
NCRR and OAR should work together to develop a mechanism for direct budgeting and tracking of AIDS research funds allocated to vaccine clinical trials.	Vaccine Research and Development pg. 52	**270 pg. 232**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
A substantial proportion of the budget assigned to AIDS vaccine clinical trials infrastructure and AIDS training requires reexamination. FIC and OAR should work together to ensure that assignment of codes for vaccine clinical trials is appropriately applied.	Vaccine Research and Development pg. 52	**271 pg. 233**	
IV. Appendices on Special Issues Appendix 1. Links to Other Panel Reports			
OAR and NCRR should make AIDS resources available through open, competitive review to investigators who seek to perform "pilot" vaccine studies. NCRR should devise a system to ensure access to animals for AIDS vaccine studies by non-RPRC investigators.	Vaccine Research and Development pg. 66	**272 pg. 234**	**36 pg. 50**
NCRR should work with OAR and research teams studying AIDS vaccine approaches to provide adequate animal resources for testing novel vaccines, both at the RPRCs as well as at other sites.	Vaccine Research and Development pg. 66	**273 pg. 234**	
NCRR should better coordinate and integrate its HIV/AIDS vaccine research activities with other ICDs to allow better planning for nonhuman primate research centers.	Vaccine Research and Development pg. 66	**274 pg. 234**	
DRUG DISCOVERY AREA REVIEW PANEL	**Drug Discovery**		
A. Basic and Applied HIV Research			
1. Support of basic and applied HIV (and all retroviral) research should be continued.	Drug Discovery pg. 2	**275 pg. 239**	**1 pg. 13**
2. Better communication is required between the Institutes and the OAR and among the specific Institutes involved in the support of basic and applied HIV-related research.	Drug Discovery pg. 2	**276 pg. 239**	**2 pg. 13**
3. The OAR should develop a system for identifying priority areas for NIH support and for encouraging new basic research activities. This could include the formation of a blue-ribbon panel that would meet at regular intervals to assess the state of the art in HIV basic and applied research and to recommend areas for future or continued focus. This panel would also consider the likelihood of private sector involvement in various areas of HIV research.	Drug Discovery pg. 2	**277 pg. 240**	

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
4.	**Investigator-initiated applications should be strongly encouraged for those areas determined to be critical research priorities. This may be accomplished by inviting key and young investigators who are not currently involved in the designated area of research (or who are involved in allied research areas) to specific workshops.**	Drug Discovery pg. 2	**278 pg. 242**	**11 pg. 11**
5.	**Mechanisms for encouraging the initial evaluation of potential lead discoveries relevant to therapeutics should be developed. ICD staff should play a key role in ensuring appropriate contact between discoverers and potential developers. This might include providing appropriate expertise; establishing contacts, as necessary, with the private sector; ensuring rapid dissemination of new data in appropriate venues; and providing support for proof-of-concept testing in animal models and in clinical trials.**	Drug Discovery pg. 2	**279 pg. 242**	
B.	**Molecular/Structural Studies**			
1.	**Continued support of structure-based designs focused on the HIV protease and reverse transcriptase (RT) should be evaluated periodically, given the commercial sector's changing interest in these targets.**	Drug Discovery pg. 3	**280 pg. 244**	
2.	**Support for new structure-based inhibitor design should focus on HIV integrase and on novel approaches to other targets, such as the CD4 receptor.**	Drug Discovery pg. 3	**281 pg. 244**	
3.	**Support should continue for structural studies of HIV envelope glycoproteins, regulatory proteins, response elements, and regulatory protein/response element complexes.**	Drug Discovery pg. 3	**282 pg. 245**	
4.	**Use of diverse funding mechanisms, including both investigator-initiated grants and targeted initiatives, should continue.**	Drug Discovery pg. 3	**283 pg. 246**	
5.	**Enhanced cooperation among ICDs for the coordination of structural studies should be ensured by OAR.**	Drug Discovery pg. 3	**284 pg. 246**	
6.	**A uniform policy should be implemented on the timely deposition and release of structural coordinates determined from NIH-supported studies (including research receiving partial NIH support).**	Drug Discovery pg. 3	**285 pg. 247**	
C.	**NIAID Drug Discovery Programs, including the National Cooperative Drug Discovery Groups (NCDDG), the Strategic Program for Innovative Research on AIDS Therapies (SPIRAT), and the AIDS Research and Reference Reagent Program**			

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
1. The NCDDG-HIV and SPIRAT programs should continue at their current level of support. However, both programs should be evaluated in the near future to assess their productivity and recommend appropriate adjustments, in a manner similar to the review initiated prior to the renewal of the NCDDG program.	Drug Discovery pg. 4	**286 pg. 249**	
2. The choice of therapeutic targets for study should be guided by an expert panel, including non-Government investigators, that periodically would assess the state of the art in HIV research. Consideration also should be given to the support of programs designed to investigate therapeutic approaches that do not necessarily advance the technological frontier but may have real potential for improving the current clinical management of HIV disease.	Drug Discovery pg. 4	**287 pg. 249**	
3. Realignment of current study sections to include appropriate expertise to evaluate translational research may be essential for assessment of investigator-initiated preclinical and proof-of-concept clinical studies.	Drug Discovery pg. 5	**288 pg. 251**	**8 pg. 17**
4. The AIDS Research and Reference Reagent Program is a valuable resource. NIH-funded investigators should be actively solicited and encouraged to provide, in a timely fashion, novel reagents to the program for potential use by other researchers.	Drug Discovery pg. 5	**289 pg. 251**	
D. Animal Models			
1. There remains a critical need for further development and optimization of animal models for HIV disease. This need is likely to become increasingly important in the future. Different animal models clearly will be required to meet different research needs. Some models are particularly well-suited for studies of pathogenesis, while others are useful for the preclinical evaluation of new therapeutic agents. It will be particularly important to support the development of a model that can be used for both types of studies.	Drug Discovery pg. 6	**290 pg. 252**	
2. NIH should strive to optimize and validate the small-animal models (e.g., various mouse and cat models) that currently appear useful for preclinical evaluation of anti-HIV compounds, to determine which (if any) of the models are predictive of efficacy and pharmacodynamic attributes in humans. Those models determined to be relevant and useful should be provided with additional infrastructure and support; support for other models should be de-emphasized.	Drug Discovery pg. 6	**291 pg. 252**	**290 pg. 252**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
3. More resources should be devoted to the development and optimization of the SIV-infected rhesus macaque model for preclinical drug evaluation *in vivo.* Additional support would be valuable for further derivation and standardization of molecularly cloned SHIV recombinants, expansion of colony size to reduce animal costs, and infrastructure for housing and research facilities.	Drug Discovery pg. 6	**292 pg. 252**	**290 pg. 252**
4. Drug discovery research involving the chimpanzee, rabbit/HIV, and SPF macaque models has not been productive. Funds for this research should be redirected.	Drug Discovery pg. 6	**293 pg. 252**	**290 pg. 252**
5. At this time, animal model research is sufficiently mature so that heavily directed research efforts by NIH program staff are inappropriate. Research funded in the future should be subjected to rigorous peer review. This can be facilitated by refocusing current study sections and ensuring that they have appropriate expertise; study section review is preferable to *ad hoc* reviews.	Drug Discovery pg. 6	**294 pg. 254**	**8 pg. 17**
6. The NCRR should ensure broad access by qualified investigators to the resources provided by the RPRCs. This may be accomplished by creating independent peer review panels to evaluate proposed research projects by both Center staff and non-Center investigators seeking access to these facilities. The infrastructure for studies that are approved for implementation at a given Center (including the supply, housing, and handling of the animals; obtaining and processing of specimens) should come from the operating budget of that Center. Competitive renewal of the Center grants should include, as a measure of productivity, a description of the Center's peer review process and its success in supporting studies initiated by non-Center investigators.	Drug Discovery pg. 6	**295 pg. 255**	**36 pg. 50**
7. Therapeutic agents that have limited effectiveness in patients with advanced HIV infection may be effective around the time of initial infection or in early stages of the disease. More research on both novel and conventional therapies in primate models should focus on these early time points.	Drug Discovery pg. 6	**296 pg. 255**	
E. NCI HIV Drug Discovery Program			
1. The DTP should no longer focus primarily on the nonselective antiviral screen.	Drug Discovery pg. 7	**297 pg. 256**	

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
2.	**The DTP management structure should be reviewed, given its apparent inability to enhance the productivity of the AIDS drug discovery effort.**	Drug Discovery pg. 7	**298 pg. 256**	**297 pg. 256**
3.	**The DTP should use its core resources to support NIH-wide antiretroviral discovery efforts by providing compounds and natural products for various screening endeavors as well as medicinal chemistry, pharmacologic, and toxicologic support as needed. Ongoing review of the DTP AIDS drug discovery program should include assessment of its ability to support the overall NIH drug discovery effort.**	Drug Discovery pg. 7	**299 pg. 256**	
4.	**DTP resources also should be used to support the efforts of other ICDs to develop treatments for opportunistic infections (OIs).**	Drug Discovery pg. 8	**300 pg. 257**	
5.	**An external scientific advisory board should be constituted to provide guidance regarding appropriate DTP support for NIH drug discovery programs. It is not cost-effective to reproduce the considerable DTP infrastructure in other ICDs.**	Drug Discovery pg. 8	**301 pg. 257**	
6.	**The operational logistics of the DTP require review and restructuring. Given the Panel's recommendations, a substantial decrease in the size and funding of the DTP's current HIV drug discovery effort may be appropriate.**	Drug Discovery pg. 8	**302 pg. 257**	**301 pg. 257**
7.	**Support is needed for research on developmental therapeutics for HIV-associated malignancies.**	Drug Discovery pg. 8	**303 pg. 258**	
F.	**Drug Discovery in Opportunistic Infections**			
1.	**Support for the NCDDG-OI program should continue at the present level.**	Drug Discovery pg. 8	**304 pg. 259**	
2.	**Even though it may be anticipated that some pharmaceutical industry support of mycobacterial research will be forthcoming, the present medical need justifies at least short-term support by NIH. However, NIAID should continue to monitor the development of new therapies (especially for *M. avium* complex) by the private sector, with the goal of redirecting funds at the appropriate time.**	Drug Discovery pg. 8	**305 pg. 260**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
3. Support for *Microsporidia*, *Cryptosporidium*, JC virus, and other pathogens that have less attractive market potential should be emphasized. In general, when projecting future needs, NIH should consider where pharmaceutical industry efforts are being placed, so that Federal funds can be used to target understudied pathogens.	Drug Discovery pg. 9	**306 pg. 260**	
4. The selection of organisms to be studied by the NCDDG system should involve several factors, including the number of Research Project Grants (RPGs) funding research on that organism, its relative importance in the clinical management of AIDS patients, and the commitment of pharmaceutical companies to research on the organism. An external advisory group could significantly assist in determining which organisms should be studied.	Drug Discovery pg. 9	**307 pg. 261**	**304 pg. 259**
5. The NIAID should be encouraged to periodically assess the overall value of individual contracts supporting OI research with respect to productivity, reliability, and user accessibility.	Drug Discovery pg. 9	**308 pg. 261**	
CLINICAL TRIALS AREA REVIEW PANEL	**Clinical Trials**		
1. Create a clinical trials coordinating group with broad scientific and community representation, including representatives of ICDs that conduct clinical trials to coordinate and facilitate inter-Institute collaboration.	Clinical Trials pg. 4	**309 pg. 265**	**28 pg. 40**
2. Create a single adult clinical trials network to replace the separate ACTG, CPCRA, DATRI (and possibly SPIRAT) programs under the auspices of the NIAID.	Clinical Trials pg. 5	**310 pg. 265**	**25 pg. 36**
3. A standard for databases for all NIH-funded HIV/AIDS clinical trials should be developed that would allow for cross-study analyses and longitudinal followup of participants.	Clinical Trials pg. 7	**311 pg. 265**	**26 pg. 36**
4. In general, all ICDs involved in HIV/AIDS clinical trials research should fully utilize and support the single NIAID-sponsored trials network described above. Each relevant ICD should contribute both scientific guidance within its area of expertise and funding support for the conduct of Phase II-IV trials rather than create anew the capacity to conduct such studies independently.	Clinical Trials pg. 8	**312 pg. 265**	**25 pg. 36**

NIH AIDS Task Force Recommendation		Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
4a.	**Future SOCA/ACTG collaborative studies should be developed that consider the other systemic manifestations of CMV disease, the potential interactions between CMV and HIV and their effect on both CMV and HIV disease progression, the antiretroviral effects of some CMV therapies, and the effect of anti-CMV therapy on CMV viral load and the development of resistance. This requires NEI support for a fully collegial interaction between the ophthalmology and infectious disease investigators.**	Clinical Trials pg. 8	**313 pg. 266**	
4b.	**The role of and level of support from NINDS for clinical trials of therapy for the neurologic manifestations of HIV/AIDS, as well as for evaluation of possible neurotoxicity, has been inadequate. The commitment of NINDS to such clinical trials should be addressed by the Institute Director.**	Clinical Trials pg. 8	**314 pg. 267**	
4c.	**NCI support of extramural trials has been limited to date. The recent initiative that created the AIDS Malignancy Consortium (AMC) in 1995 for the exploration of innovative Phase I/II pilot studies is underfunded. Although additional support for HIV virologic and immunologic testing has been promised by NCI, it remains to be seen whether this is a viable Phase I/IIA research program at the current level of funding. Innovative therapeutic approaches that emerge from this program will require large randomized comparative trials for confirmation. With additional fiscal and scientific support from NCI, Phase IIB/III studies could be performed in the proposed adult trials network.**	Clinical Trials pg. 9	**315 pg. 268**	
4d.	**NIMH should be encouraged to support exploratory trials for the treatment of neurocognitive and psychiatric disorders in adults and children. In the future, comparative studies in adults should be conducted by the proposed integrated network with specific scientific and fiscal support from the NIMH.**	Clinical Trials pg. 9	**316 pg. 269**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
4e. Every effort should be made to avoid competition and redundancy between the intramural and extramural programs. The intramural trials efforts should capitalize on the unique capabilities of the NIH Clinical Center and on the specific expertise of the sponsoring ICD. The Clinical Center provides the opportunity to bring patients to a single center for clinical investigation at no cost, including travel expenses, to the trial participants. This level of patient support is not routinely available even at excellent university medical centers with NIH-funded General Clinical Research Centers (GCRCs).	Clinical Trials pg. 9	**317 pg. 271**	
5. The Panel recommends that Institutes with a disease-specific (e.g., NCI) or an organ system-specific focus (e.g., NEI, NINDS, NIDDK) be responsible scientifically and fiscally for clinical trials specific to their mandate. Scientific priorities and consequent funding of the various intramural clinical trials efforts should be carefully scrutinized by each Institute Director.	Clinical Trials pg. 9	**318 pg. 272**	**13 pg. 22**
6. The Panel unequivocally supports the need for greater balance between investigator-initiated grants and targeted initiatives for support of clinical trials. Small-scale trials can and should be supported by individual grants.	Clinical Trials pg. 10	**319 pg. 272**	
7. Adequate and appropriate scientific review of proposed clinical trials programs—regardless of funding mechanism—must involve the most qualified, knowledgeable scientists.	Clinical Trials pg. 10	**320 pg. 272**	**7, 8, 319 pgs. 16, 17, 272**
8. NIH and industry efforts should be coordinated. NIH studies should be undertaken that extend our knowledge of disease processes as well as assess the impact of therapy, which is typically not the focus of industry-sponsored trials.	Clinical Trials pg. 10	**321 pg. 274**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
9. The Panel did not dissect in detail the scientific agenda of each clinical trials program. These issues have been the subject of other targeted reviews. However, the Panel did recognize cross-cutting areas that should be of high priority. These include: (1) validation of surrogate endpoints as markers of clinical outcome, (2) utilization of aggressive combination therapies for all stages of HIV infection, including treatment of primary HIV infection (acute seroconversion), (3) elimination of HIV transmission from mother to fetus, (4) continued progress in the management and prevention of OIs, (5) HIV-associated malignancies, (6) HIV-associated neurologic complications, (7) immunologic interventions, (8) management of wasting syndrome, and (9) elaboration of the natural history components of therapeutic studies (e.g., mucosal shedding of HIV, the contribution of OIs to HIV progression, and long-term followup of unique cohorts of HIV-infected individuals who have participated in therapeutic studies). Furthermore, the feasibility of the interdigitating assessment of behavioral and medical endpoints should be evaluated.	Clinical Trials pg. 11	**322 pg. 275**	
10. Better definitions of AIDS and AIDS-related research must be established so that AIDS funds are appropriately allocated. An improved database at the NIH is critical to both the management of NIH fiscal resources and the tracking of research progress.	Clinical Trials pg. 11	**323 pg. 276**	**44 pg. 65**
AD HOC PANEL ON COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES RESEARCH	**Complementary and Alternative Medicine Therapies Research**		
1. The OAR should establish an ongoing advisory panel on CAM for HIV disease to help identify and distinguish therapies with apparent promise from those with potential harm. This panel should be comprised of scientists experienced in HIV and/or CAM research and individuals involved in the use of alternative therapies.	Complementary and Alternative Medicine Therapies Research pg. 2	**324 pg. 279**	
2. The OAR, in collaboration with its HIV-CAM Advisory Panel, should work in partnership with the NIH Office of Alternative Medicine (OAM) to establish an operational definition of complementary and alternative therapies for HIV disease and to construct a taxonomy to categorize therapies in this area.	Complementary and Alternative Medicine Therapies Research pg. 2	**325 pg. 279**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
3. Once a definition of complementary and alternative therapies is developed, the OAR should sponsor a survey on the current use of these therapies by persons living with HIV. This survey should include participants in NIH-sponsored clinical trials and natural history cohorts.	Complementary and Alternative Medicine Therapies Research pg. 3	**326 pg. 279**	
• **The Panel believes the following to be important and necessary to the successful consideration of HIV-related CAM approaches for research funding: An operational definition of CAM as it relates to HIV disease, collaboratively derived by the OAR, the OAM, and appropriate representatives from the HIV-affected and CAM scientific community, and used throughout the NIH in budgetary and research planning of its AIDS program.**	Complementary and Alternative Medicine Therapies Research pg. 3	**327 pg. 279**	**326 pg. 279**
• **The identification and prioritization of HIV-CAM research approaches for agents that:** ∘ **Are widespread in use or potentially may come into widespread use (in the United States and abroad);** ∘ **Can be accessed easily and used by underserved populations;** ∘ **Have large potential impact on the HIV-infected community;** ∘ **Have extremely low or high potential harm;** ∘ **Show scientific rationale;** ∘ **Are potentially cost-effective or costly; and** ∘ **Have potential for self-care.**	Complementary and Alternative Medicine Therapies Research pg. 3	**328 pg. 280**	**326 pg. 279**
• **The field of HIV-CAM research will benefit as a whole if alternative medicine investigators acquire greater familiarity with and experience in conventional medical research methodology.**	Complementary and Alternative Medicine Therapies Research pg. 3	**329 pg. 281**	
4. The OAR and the HIV-CAM Advisory Panel should work in partnership with the OAM to sponsor workshops on the research methods appropriate for the evaluation of CAM therapies for HIV disease. The utility of available methods and their limitations should be reviewed, and approaches to strengthen their scientific basis should be identified. Participants in these workshops should include representatives from OAR, OAM, the ICDs, the Food and Drug Administration (FDA), and CAM practitioners and researchers as well as HIV-infected persons who use CAM therapies.	Complementary and Alternative Medicine Therapies Research pg. 3	**330 pg. 281**	**329 pg. 281**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
5. The OAR should help facilitate linkages between persons interested in the evaluation of CAM therapies for HIV disease and investigators with experience in designing clinical trials or laboratory investigations.	Complementary and Alternative Medicine Therapies Research pg. 4	**331 pg. 281**	**329 pg. 281**
6. The OAR should, where appropriate, work with and provide supplemental funding to support OAM research activities and program goals in the area of HIV disease.	Complementary and Alternative Medicine Therapies Research pg. 4	**332 pg. 281**	
7. The OAR should work with the OAM to sponsor workshops to educate individuals interested in the evaluation of candidate CAM therapies for HIV disease about the preparation of NIH grant applications and the processes by which such applications are evaluated.	Complementary and Alternative Medicine Therapies Research pg. 4	**333 pg. 282**	
8. The OAR should work with the OAM and the DRG to suggest individuals who may serve as *ad hoc* members of study sections that are considering applications concerning CAM therapies for HIV disease. Criteria for the selection of *ad hoc* study section members should include those currently used by DRG as well as experience in the scientific evaluation of novel therapeutic approaches and a familiarity with the concepts and practices of CAM therapies.	Complementary and Alternative Medicine Therapies Research pg. 5	**334 pg. 282**	
AD HOC SUBPANEL ON OPPORTUNISTIC INFECTIONS RESEARCH SUBGROUPS REPORT	**Opportunistic Infections Research**		
1. Reinvigorate the basic science research effort on AIDS-associated OIs. **A. The highest priority of the NIH effort in OI research should be basic scientific studies of organism life cycles, metabolism, transmission, epidemiology, pathogenesis, and host response.**	Opportunistic Infections Research pg. 2	**335 pg. 285**	
• The NIH should stimulate progress in these areas by support of investigator-initiated grants that encourage collaboration between basic research scientists and between basic research scientists and clinical investigators. **• The NIH should structure funding mechanisms in such a way to diminish the complexity of the grant application process (e.g., requirements that collaborators be at different institutions or that industrial collaborations be established) and maximize the process of scientific discovery.**	Opportunistic Infections Research pg. 2	**336 pg. 285**	

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **The NIH should encourage research into the pathogenesis of opportunistic diseases in their natural hosts and in relevant animal model systems.**	Opportunistic Infections Research pg. 2	**337 pg. 287**	**335 pg. 285**
• **A program of small pilot grants should be implemented to support preliminary projects of high risk but significant potential promise. The intent of these grants (e.g., approximately $50,000 per year for 1 to 2 years) would be to test a principle or gather sufficient preliminary data for submission of an R01 grant application.**	Opportunistic Infections Research pg. 2	**338 pg. 287**	**336 pg. 285**
B. The NIH currently supports an active program of research in this area, and it is expected that the productivity of this effort will be enhanced significantly by the recommendations discussed elsewhere in this report, including those that call for the following:			
• **increased support for investigator-initiated research,**	Opportunistic Infections Research pg. 2	**339 pg. 287**	**1 pg. 13**
• **expert peer review informed of the scientific priorities of the annual NIH Plan for HIV-Related Research,**	Opportunistic Infections Research pg. 2	**340 pg. 288**	**6 pg. 15**
• **increased efforts to encourage young investigators to enter AIDS research, and**	Opportunistic Infections Research pg. 2	**341 pg. 288**	**11 pg. 18**
• **increased efforts to attract established investigators with expertise in related areas to pursue AIDS-related research.**	Opportunistic Infections Research pg. 2	**342 pg. 288**	**12 pg. 21**
C. To further progress in this area, the Office of AIDS Research (OAR) and relevant Institutes, Centers, and Divisions (ICDs) should increase and better coordinate their efforts to foster research on AIDS-related OIs and continue to solicit the advice of non-Government scientists in identifying new research needs and opportunities in this area. As many of the AIDS-associated OIs also cause disease in individuals with other types of immunodeficiency and research on these pathogens is consequently supported with both AIDS and non-AIDS funds, it will be important to view the NIH portfolio in this area as defined by scientific issue rather than funding mechanism.			

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **The OAR should establish an external expert advisory group to advise the OAR concerning evolving opportunities and needs in AIDS OI research. This group should review the NIH OI research portfolio on a yearly basis and recommend adjustments for programs that need to be updated or changed. This group should encourage improved reportability and accountability of programs sponsored by various ICDs. A consistent standard for high-quality science should be emphasized, and indicated resources should be redirected away from less productive programs. Many AIDS-associated OIs also cause disease in persons with other types of immunodeficiency, and research on these infections is supported with both AIDS-designated and non-AIDS funds; thus, the advisory group should monitor the NIH's OI research portfolio as a whole rather than only that portion supported by AIDS-designated resources. This approach will ensure better overall assessment and coordination of NIH's OI research activities.**	Opportunistic Infections Research pg. 3	**343 pg. 288**	
• **Existing NIH databases of funded research activities are inadequate for assessment of funds supporting OI research. The NIH should improve the data management and retrieval systems for ongoing research. The NIH data bases should be structured to permit greater ease of accessibility and be updated on a regular basis.**	Opportunistic Infections Research pg. 3	**344 pg. 290**	**43 pg. 62**
• **The OAR, in collaboration with the relevant ICDs and industry representatives, should establish a regular review of OI research by sponsoring focus meetings on individual pathogens and on groups of related pathogens. This process should result in the development of goals that are jointly recognized by academic, Government, and industry scientists and will facilitate greater communication of relevant results and more rapid exploitation of research opportunities.**	Opportunistic Infections Research pg. 3	**345 pg. 291**	
D. The NIH should take a more productive approach to training of scientists for the study of OIs. At present, the Subpanel believes the following:			
• **There is at present a crisis in the relative lack of incentives to enter the field of OI research and inadequate opportunities and support to train young investigators in OI research.**	Opportunistic Infections Research pg. 3	**346 pg. 291**	**11-13 pgs. 18-22**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **The NIH should undertake to make it easier for young investigators to obtain initial NIH research support. Possible approaches might include a separate review process for R29 grants or more generous funding levels for these applications. Establishment of a program of short-term (1 to 2 years) grants to provide initial support to promising young scientists should also be considered.**	Opportunistic Infections Research pg. 3	**347 pg. 292**	**11, 346 pgs. 18, 291**
• **The NIH should continue to enhance training programs that encourage young scientists to pursue research on OIs. In addition, funding support should be considered for established investigators in one field to retrain in a laboratory studying opportunistic pathogens, and for young investigators within mentorship programs.**	Opportunistic Infections Research pg. 3	**348 pg. 292**	**11-13, 346 pgs. 18-22, 291**
• **The NIH should sponsor short courses (3 to 4 weeks) on opportunistic pathogens to attract young investigators as well as established investigators working in related fields to pursue research on AIDS-associated OIs.**	Opportunistic Infections Research pg. 4	**349 pg. 292**	
2. The NIH should pursue innovative approaches to foster the transfer of new laboratory findings to early "proof of principle" clinical evaluation. **The OI Subpanel suggests the following strategies to accomplish this goal:**			
• **The OAR should facilitate the translation of promising basic research findings to clinical applications. A translational research coordinator within the OAR, and informed by the external advisory panel on OIs described above, should work with basic scientists and industry to identify promising opportunities in their areas and help establish productive collaborative efforts.**	Opportunistic Infections Research pg. 4	**350 pg. 293**	
• **The OAR should work with the ICDs and the Small Business Administration to improve the quality and impact of AIDS-related research funded by the NIH through the Small Business Innovative Research (SBIR) grant program. These funds should be focused on important unmet needs in AIDS research through a new program of Request for Applications (RFAs) issued to small biotech or pharmaceutical firms. The topics of these RFAs should be defined by OAR and ICD staff members, in consultation with Government and non-Government scientists, to target emerging opportunities for the development of diagnostics and therapeutics for HIV infection and its associated complications.**	Opportunistic Infections Research pg. 4	**351 pg. 294**	**31 pg. 45**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **The NIH should strengthen the study sections that review SBIR grants related to AIDS with respect to scientific expertise and familiarity with contemporary scientific needs and opportunities, as articulated in the annual NIH Plan for HIV-Related Research.**	Opportunistic Infections Research pg. 4	**352 pg. 295**	**7 pg. 16**
• **The Area Review Panel evaluating the Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI) should consider the potential contribution of the program to identify and produce candidate agents for the treatment of OIs for which there is little or no interest within the pharmaceutical industry. Should the AIDS-related activities of the DTP program be continued in the future, they may provide a vehicle to advance candidate drugs from the research laboratory to a stage where an Investigational New Drug (IND) application can be filed with the Food and Drug Administration (FDA), permitting initial clinical evaluation. Should promising agents be identified in "proof of concept" clinical trials, it is likely that the interest of the pharmaceutical companies in further developing such agents may be increased substantially.**	Opportunistic Infections Research pg. 4	**353 pg. 295**	
Outstanding Research Needs in Specific Areas			
I. ***Pneumocystis carinii***			
• **Basic studies elucidating the beneficial or deleterious roles of the host immune responses directed against PCP, the effects of the organism on lung physiology, and basic research for antigenic and serologic reagents are recommended. The development of immunotherapies and vaccines should proceed more rapidly based on the results of these studies. Research leading to a clearer understanding of the establishment of infection (e.g., the role of organism attachment to host cells) is recommended.**	Opportunistic Infections Research pg. 8	**354 pg. 297**	
• **The pathology that PC exerts on the host remains poorly understood, yet the development of effective prophylaxis or therapeutic measures will likely be greatly expedited by understanding better the response of both the immune-competent and immunosuppressed hosts to the organism.**	Opportunistic Infections Research pg. 8	**355 pg. 297**	**354-404 pgs. 297-305**
• **The Subpanel recommends that research leading to a clearer understanding of the establishment of infection (e.g., the role of organism attachment to host cells) be emphasized.**	Opportunistic Infections Research pg. 8	**356 pg. 297**	**354-404 pgs. 297-305**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **The Subpanel recommends supporting research to develop a noninvasive diagnostic test that would discriminate between acute-phase infection, remote infection, or exposure.**	Opportunistic Infections Research pg. 8	**357 pg. 297**	**354-404 pgs. 297-305**
• **Development is needed of a rapid noninvasive diagnostic test that would discriminate between acute-phase infection and remote infection or exposure.**	Opportunistic Infections Research pg. 9	**358 pg. 297**	**354-404 pgs. 297-305**
• **The Subpanel recommends support for the development of therapeutic and prophylactic modalities. A goal should include an identification of a battery of agents, including combinations of chemotherapeutic and immunotherapeutic agents, to prevent the emergence of drug-resistant organisms.**	Opportunistic Infections Research pg. 9	**359 pg. 297**	**354-404 pgs. 297-305**
• **Research is needed to develop strategies to detect drug resistance and identify mechanisms of resistance used by the organism.**	Opportunistic Infections Research pg. 10	**360 pg. 297**	**354-404 pgs. 297-305**
• **It is critical to revise current mechanisms for introducing candidate compounds identified through drug-screening programs into safety and tolerance trials followed by efficacy evaluation. Suggestions include an OAR-affiliated translational research coordinator working with expert external advisors to select promising drugs from basic OI research for clinical development and to oversee the early transition of those candidate agents into efficacy evaluations.**	Opportunistic Infections Research pg. 10	**361 pg. 297**	**354-404 pgs. 297-305**
II. Fungal Infections			
• **Serial studies of the incidence, prevalence, and clinical course of at-risk patients of different age groups for a variety of fungi such as *Candida, Pneumocystis, Cryptococcus, Aspergillus, Histoplasma, Coccidioides,* etc., are necessary.**	Opportunistic Infections Research pg. 11	**362 pg. 298**	**354-404 pgs. 297-305**
• **Investigations of the basic molecular pathobiology of fungi should be encouraged and supported. It will be important to attract molecular biologists currently conducting research in other eukaryotic systems to interact with mycologists who understand clinical disease.**	Opportunistic Infections Research pg. 12	**363 pg. 298**	**354-404 pgs. 297-305**

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
• **The NIH should encourage development of reliable methods for the rapid diagnosis of infection using nucleic acid or protein-based detection strategies and should coordinate this work with industry.**	Opportunistic Infections Research pg. 12	**364 pg. 298**	**354-404 pgs. 297-305**
• **The NIH should support basic science initiatives to identify drug targets, drug-resistance mechanisms, animal models, clinical strategies of treatment and prophylaxis, and immune modulation.**	Opportunistic Infections Research pg. 13	**365 pg. 298**	**354-404 pgs. 297-305**
III. Viral Infections			
1. CMV, HSV, VZV: Identify and understand mechanisms of viral latency, including the viral and host functions that restrict viral productive replication. Investigate viral genes controlling dissemination, tissue invasion and disease following reactivation, and the relationship of disease to immunodeficiency. Investigate host cell functions that restrict intracellular viral replication. Understanding these functions will provide additional targets for antiviral therapy and vaccine development. Investigate mechanisms of drug resistance and the impact of drug resistance mutations on pathogenesis in animal models and in patients.	Opportunistic Infections Research pg. 15	**366 pg. 298**	**354-404 pgs. 297-305**
2. KSHV: Identify viral genetic determinants causing cell proliferation and their effect on the host cell. Determine the cellular and molecular events that lead to proliferation and the cell types involved.	Opportunistic Infections Research pg. 15	**367 pg. 299**	**354-404 pgs. 297-305**
3. EBV: Understand the mechanisms of EBV-induced lymphocyte proliferation. Studies should be aimed at the function of latent gene products and their interaction with cellular signaling pathways as well as on ways to use this information to control proliferation and understand the particular determinants associated with lymphoproliferative disease.	Opportunistic Infections Research pg. 16	**368 pg. 299**	**354-404 pgs. 297-305**
4. Other viruses: Investigation of the viral and host genetic basis of how viral persistence, immune response, or the damage to specific tissues leads to disease.	Opportunistic Infections Research pg. 16	**369 pg. 299**	**354-404 pgs. 297-305**
Immune Control			

NIH AIDS Task Force Recommendation	Page Number Where Recommendation Appears in the Task Force Report	Recommendation Number Assigned for the Implementation Plan Report	Implementation Report Cross-References to Other Recommendations
1. Understanding mechanisms of immune control **a. productively infected cells: CMV, HSV, VZV, HHV-6, HHV-7, JCV, hepatitis viruses** **b. latently infected cells: CMV, KSHV, EBV, HPV, HSV, VZV, HHV-6, HHV-7, JCV, hepatitis viruses** **c. proliferating cells: KSHV, EBV, HPV**	Opportunistic Infections Research pg. 16	**370 pg. 299**	**354-404 pgs. 297-305**
2. Identification of viral antigen targets of immune control. Determine the spectrum of antigens that are required for the induction of protective viral immunity	Opportunistic Infections Research pg. 16	**371 pg. 299**	**354-404 pgs. 297-305**

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3. Understanding the contribution of the host immune response to disease (immunopathology)	Opportunistic Infections Research pg. 16	**372 pg. 299**	**354-404 pgs. 297-305**
• More work on the patterns of viral gene expression or antibodies needs to be completed in order to have diagnostic tests that are predictive of disease and that can be used to make informed choices in therapy. Diagnostic tests need to be developed that can be applied to readily accessible cells or fluids. Development of rapid standardized methods to identify infections with drug-resistant viruses is needed.	Opportunistic Infections Research pg. 16	**373 pg. 299**	**354-404 pgs. 297-305**
IV. Mycobacterial OIs			
Mycobacterium tuberculosis			
• TB research must be accorded the highest priority by the NIH. TB is not simply a U.S. problem or an HIV-related problem. TB cannot be controlled in this country until it is controlled worldwide. The current level of NIH funding of TB research is appropriate given the public health importance, clinical needs, and the scientific opportunities.	Opportunistic Infections Research pg. 21	**374 pg. 300**	**354-404 pgs. 297-305**
• To optimize research efforts on TB, increased coordination is required at multiple levels: within the PHS (NIH and CDC), among the NIH Institutes, and within NIAID (DMID, DAIDS) as well as with other funding agencies (WHO). This coordination must be sustained and enhanced, independent of the current high level of public and political interest.	Opportunistic Infections Research pg. 21	**375 pg. 300**	**354-404 pgs. 297-305**
• The NIH should give special consideration to ensuring that successful research projects and programs are sustained. The flurry of RFAs and RFPs has galvanized the scientific community. This impressive effort will, however, stall unless special consideration commensurate with the importance of this topic is accorded to the review process for competitive renewals.	Opportunistic Infections Research pg. 21	**376 pg. 300**	**354-404 pgs. 297-305**
• Scientific areas of particular importance include studies of fundamental mechanisms of drug resistance and drug action, new drug targets, latency, and protective immunity. The NIH should give a high priority to basic and applied research on TB vaccine development.	Opportunistic Infections Research pg. 21	**377 pg. 300**	**354-404 pgs. 297-305**

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• **To increase our understanding of TB and develop new drugs, a comprehensive effort is essential to address and resolve the disincentives to pharmaceutical companies, given the low incidence of TB in the United States.**	Opportunistic Infections Research pg. 21	**378 pg. 300**	**354-404 pgs. 297-305**
• **The NIH should redirect major clinical trials efforts to international sites in areas of high incidence of TB (and HIV).**	Opportunistic Infections Research pg. 21	**379 pg. 300**	**354-404 pgs. 297-305**
Mycobacterium avium			
• **The NIH should convene a consensus panel to review current research activities and scientific opportunities concerning MAC. The NIH should develop an expanded scientific agenda through RFAs and Program Announcements.**	Opportunistic Infections Research pg. 23	**380 pg. 301**	**354-404 pgs. 297-305**
• **The NIH should encourage research in the areas of protective immunity, pathogenesis, mechanisms of drug resistance, and identification of new drug targets.**	Opportunistic Infections Research pg. 23	**381 pg. 301**	**354-404 pgs. 297-305**
• **The NIH should address the issue of protective immunity in humans through epidemiologic studies in areas of high and low prevalence of disseminated MAC in AIDS patients.**	Opportunistic Infections Research pg. 23	**382 pg. 301**	**354-404 pgs. 297-305**
V. ***Toxoplasma gondii***			
• **There is little understanding of the role that parasite-versus-host genotypes play in disease, and it remains unclear why toxoplasmosis develops in only a subset of patients. Further research is needed to define the relationship of both the parasite and host genotypes to disease pathogenesis and clinical outcomes.**	Opportunistic Infections Research pg. 24	**383 pg. 301**	**354-404 pgs. 297-305**
• **Research is needed to carefully define the contribution clonal type may play in determining differences with respect to drug sensitivity, virulence, and immune response.**	Opportunistic Infections Research pg. 24	**384 pg. 301**	**354-404 pgs. 297-305**
• **There is an urgent need to define fundamental metabolic pathways of the parasite, especially bradyzoites. Little is known about the basic metabolism of tachyzoites, and even less is known about the metabolic processes of bradyzoites. Intermediary metabolism studies are needed to define what pathways are present and how they differ from the mammalian host. Research in this area is needed and represents the best hope of ultimately identifying new targets and new therapies. As such, it deserves high priority.**	Opportunistic Infections Research pg. 24	**385 pg. 301**	**354-404 pgs. 297-305**

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• **The host-parasite interaction is a critical area for future investigation.** **a. Research on the parasite cytoskeleton and on the mechanism of motility is warranted, given the involvement of the parasite cytoskeleton in host cell invasion.** **b. Characterizing the process of parasite secretion and defining the biological function of secreted proteins are essential for understanding the mechanism of intracellular infection. These studies will likely define new targets for therapeutic intervention.** **c. Research is necessary to increase understanding of the role that specific *T. gondii* genes play in virulence. Knowledge of these genes should provide the foundation necessary to develop new therapies and/or vaccines.** **d. Research is needed to identify and characterize genes involved in stage conversion from tachyzoite to bradyzoite or that are necessary for intracellular replication. The identification of essential gene functions will help define novel therapeutic targets.** **e. Although host genetic factors in murine and human systems are partially identified, there is a need to determine how chronic infection is established and how it may be modulated by the host immune system. The area that is the least clear, and one for which continued attention is needed, is definition of the combination of factors (parasite strain, host genetic background, immunologic components) that are involved in the reactivation of disease.**	Opportunistic Infections Research pg. 25	**386 pg. 301**	**354-404 pgs. 297-305**
• **Further development of stable episomal vectors, or those with inducible promotors, and of new strategies to disrupt essential genes or otherwise genetically manipulate these parasites is needed in order to better understand their biology. Research efforts should be devoted to developing those tools. Construction of new libraries should also be supported to further define the genetic constituents of these pathogens and the genes they express at different stages of their life-cycles. The continued lack of an axenic culture system confounds mutant generation and recovery, and the NIH should support efforts to identify axenic culture conditions.**	Opportunistic Infections Research pg. 25	**387 pg. 302**	**354-404 pgs. 297-305**

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• **Improved diagnostic tools are needed, but it is likely that there will be no simple solutions to the problem of distinguishing active from chronic infection. It is not obvious that PCR-based assays are the answer, and new approaches in this area are needed.**	Opportunistic Infections Research pg. 25	**388 pg. 302**	**354-404 pgs. 297-305**
• **Newly available monoclonal antibodies to parasite antigens as well as cloned genes expressed as recombinant full-length and/or fusion proteins could be used to develop assays and reagents for detection of specific parasite antigens in infected individuals.**	Opportunistic Infections Research pg. 26	**389 pg. 302**	**354-404 pgs. 297-305**
• **High-throughput screens for microbicidal drugs should be applied to both tachyzoites and bradyzoites, using new systems developed for *in vitro* bradyzoite generation and for automated monitoring of parasite growth. These screens are probably best done by the pharmaceutical industry, with input from scientists in academia, although this may not be realistic without more active encouragement of industry involvement. Since eradication of bradyzoites within tissues would eliminate the risk of recurrence from recrudescent disease, identification of drugs with this spectrum of activity is a particularly attractive goal. The development of conditions for *in vitro* differentiation of tachyzoites from bradyzoites, of stage-specific reagents, of transgenic parasites stably expressing enzyme markers (such as β-galactosidase), and of molecular genetic tools is likely to have a major impact on this priority. There also is no substitute for continued screening of promising compounds *in vivo*, since there are discrepancies between the utility of drugs *in vitro* and *in vivo* for *T. gondii*, at least in part due to differences in *in vitro* assay methodology.**	Opportunistic Infections Research pg. 26	**390 pg. 303**	**354-404 pgs. 297-305**
• **New drug targets should be identified through the definition of metabolic pathways, targeted sequencing efforts, further definition of the cell biology of invasion and intracellular infection, and new molecular approaches, including mutant generation.**	Opportunistic Infections Research pg. 26	**391 pg. 303**	**354-404 pgs. 297-305**

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• **A human vaccine for *T. gondii* is neither practical nor appropriate. Vaccination of meat animals that represent an important source of human infection is, however, a viable approach because (1) such a vaccine can reasonably be tested for efficacy, (2) it would have its own market (*T. gondii* causes spontaneous abortion in sheep), (3) a great deal is known about how to formulate animal vaccines, and (4) such animals are kept under semicontrolled conditions. Although this research would not have immediate benefits, such an approach could ultimately massively reduce the number of chronically infected persons at risk for reactivation.**	Opportunistic Infections Research pg. 26	**392 pg. 303**	**354-404 pgs. 297-305**
• **The relative contribution to human infection of oocysts (in cat feces) versus tissue cysts (in undercooked meat) needs clearer definition. This information should be incorporated into proactive public health education programs that transmit the message that toxoplasmosis is a problem and infection with *Toxoplasma* is worth avoiding. Wide dissemination of simple recommendations to prevent acquisition of toxoplasmosis could ultimately have a wide impact in lowering the infected population at risk for reactivation.**	Opportunistic Infections Research pg. 27	**393 pg. 303**	**354-404 pgs. 297-305**
VI. *Cryptosporidium* and the *Microsporidia* OIs			
• **Epidemiologic studies are needed to determine the true incidence of these infections in HIV-infected persons and the threat that they represent to the general population. Basic questions of host range and specificity along with transmission routes need to be determined for the *Microsporidia*.**	Opportunistic Infections Research pg. 28	**394 pg. 304**	**354-404 pgs. 297-305**
• **Determine whether isolate/strain variation for *Cryptosporidium* exists and if this impacts on pathogenic potential. Develop isolate-specific PCR probes to distinguish isolated strains.**	Opportunistic Infections Research pg. 28	**395 pg. 304**	**354-404 pgs. 297-305**
• **Develop and improve both *in vitro* and *in vivo* models that can be used to address issues of basic organism biology and pathophysiology, immune responsiveness, prophylaxis and therapy, and differential parasite life cycle stage production. This remains the highest priority of research in this area.**	Opportunistic Infections Research pg. 29	**396 pg. 304**	**354-404 pgs. 297-305**
• **Determine molecular and pathophysiologic mechanisms of disease and explore potential treatments directed at amelioration of deranged physiology.**	Opportunistic Infections Research pg. 29	**397 pg. 304**	**354-404 pgs. 297-305**

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• **Gain a more fundamental knowledge of the host-parasite relationship during *Cryptosporidium* infection and better characterize immune responsiveness in both immunocompetent and immunocompromised hosts. In addition, determine if latent infections occur.**	Opportunistic Infections Research pg. 29	**398 pg. 304**	**354-404 pgs. 297-305**
• **Diagnostic methods are desperately needed for the *Microsporidia* and more economical tests are needed for *Cryptosporidium*.**	Opportunistic Infections Research pg. 29	**399 pg. 304**	**354-404 pgs. 297-305**
• **Enhanced detection methods to determine viability of the *Cryptosporidium* oocyst in water are needed in order to evaluate new paradigms of water treatment.**	Opportunistic Infections Research pg. 29	**400 pg. 304**	**354-404 pgs. 297-305**
• **Identify molecular and biochemical targets for chemotherapeutic and immunotherapeutic approaches to controlling infection.**	Opportunistic Infections Research pg. 29	**401 pg. 304**	**354-404 pgs. 297-305**
• **Give strong consideration to the development of *Cryptosporidium* vaccination strategies that might enhance mucosal responsiveness in humans or control infections in domestic livestock, which could serve as a source of infection to humans.**	Opportunistic Infections Research pg. 29	**402 pg. 305**	**354-404 pgs. 297-305**
• **Support development of centralized facilities for the production, purification, distribution, and potential cryopreservation of parasites. To some extent, this may impact the desirability for a standardization of *in vitro* and *in vivo* model systems.**	Opportunistic Infections Research pg. 30	**403 pg. 305**	**354-404 pgs. 297-305**
• **Provide realistic funding support in terms of amount and time to conduct the above research and commit to bring bright, young, energetic investigators into this arena of research.**	Opportunistic Infections Research pg. 30	**404 pg. 305**	**354-404 pgs. 297-305**
VII. Opportunistic Infections in Pediatric Patients			
• **A specific focus on pediatric OIs is required, since there are both epidemiologic and microbiologic features that distinguish pediatric infections from those manifest in adulthood.**	Opportunistic Infections Research pg. 31	**405 pg. 311**	
• **Lengthened survival due to improvements in antiretroviral therapy and adjuvant measures should facilitate the study of acquisition, natural history, pathogenesis, and modes of intervention in OIs that are unique to pediatric HIV infection.**	Opportunistic Infections Research pg. 31	**406 pg. 311**	**405 pg. 311**
• **Studies must be performed in children to better understand and treat infectious complications in this unique group of patients with AIDS.**	Opportunistic Infections Research pg. 31	**407 pg. 311**	**405 pg. 311**

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VIII. Emerging/Unrecognized Pathogens			
• **The NIH needs to support broad-based innovative molecular and culture-based investigations to identify previously unrecognized opportunistic pathogens in HIV-infected persons. Certain unexplained clinical syndromes, such as those mentioned above, should be targeted. Particularly promising experimental approaches include consensus PCR amplification of conserved, phylogenetically useful microbial sequences (e.g., ribosomal DNA), and representational difference analysis (RDA). Careful selection of clinical samples and appropriate controls is critical (see the next recommendation). In the absence of proof of Koch's postulates, special attention should be placed upon data that support a causal association between molecular information and pathology. The NIH must recognize and accept the relatively high-risk nature of such investigations. Two-year, $150,000 to $200,000 pilot-feasibility grants may be a useful funding approach.**	Opportunistic Infections Research pg. 32	**408 pg. 313**	**354-404 pgs. 297-305**
• **There is a need for the NIH to establish a clinical specimen bank (body fluids and tissues) from HIV-infected persons with designated syndromes of unknown but potentially infectious etiology. Specimens containing suspected pathogens, or isolates that resist identification should also be collected. The specimen bank(s) should include matched specimens as controls. The bank(s) would serve as repositories of samples for which qualified investigators could apply for access. Carefully procured and catalogued specimens of this type are difficult to secure and, as a widely available valuable resource, would encourage more numerous and productive investigations of new putative pathogens. The ACTG network might offer an attractive source of samples. For example, bronchoscopic, endoscopic, liver, lymph node, and whole blood samples might be identified, catalogued, and saved during the course of multicenter protocols. One of the advantages of a well-established network such as the ACTG is that critical clinical information and followup data would be available for correlation with molecular data. Actual, prospective "real-time" specimen collection will be necessary to track sporadic or unanticipated clinical syndromes; donor identification alone might be sufficient with later specimen collection for unexplained but common clinical syndromes.**	Opportunistic Infections Research pg. 33	**409 pg. 313**	

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• **The NIH should collaborate with and lend support to the CDC's Emerging Infections program. This program currently comprises four regional centers (in Connecticut, Minnesota, Oregon, and California) devoted to epidemiologic surveillance and analysis of unexplained critical illnesses and deaths in HIV-negative hosts. A similar network should be established for epidemiologic surveillance and laboratory investigation of unexplained critical illnesses and deaths in HIV-infected persons. The NIH should encourage this type of program for HIV-infected persons from regions of the world with high HIV endemicity.**	Opportunistic Infections Research pg. 33	**410 pg. 314**	
• **There is a need to address the following issues regarding specific pathogens: KSHV—risk factors for infection and disease, reservoir, virus population structure, origins of the virus, mechanisms of transmission, incubation period, host immune response to infection and disease, and role in other diseases; B. henselae—mechanisms of transmission, geographic and temporal fluctuations in disease prevalence, and population structure; *Cyclospora*—relative importance as cause of chronic diarrhea in HIV-infected persons.**	Opportunistic Infections Research pg. 33	**411 pg. 315**	**354-404 pgs. 297-305**
• **The NIH should fund basic laboratory investigations of pathogenic mechanisms used by recently identified opportunistic pathogens in HIV-infected persons.**	Opportunistic Infections Research pg. 34	**412 pg. 315**	**354-404 pgs. 297-305**
• **Interactions between HIV and recently identified opportunistic pathogens should be explored. In addition, the contributions of one opportunistic microbial agent to the pathogenicity of another agent may be an important area for study.**	Opportunistic Infections Research pg. 34	**413 pg. 315**	**354-404 pgs. 297-305**
• **The impact of HIV infection on the composition of the host commensal microbial flora should be evaluated as an important source of emerging pathogens.**	Opportunistic Infections Research pg. 34	**414 pg. 315**	**354-404 pgs. 297-305**
• **The following issues should be addressed regarding specific pathogens: KSHV and *B. henselae*—association of specific clones with angioproliferation or transformation, mechanisms of pathogen-associated angiogenesis or oncogenic transformation, mechanisms of cellular and tissue tropism, development of animal models, role of host cytokines and immune responses in causation of disease and host pathology, ability of a pathogen to modulate host responses; KSHV—development of methods for cultivation, assessment of latency; *B. henselae*—differential host tissue response in immunocompromised versus immunocompetent hosts.**	Opportunistic Infections Research pg. 34	**415 pg. 316**	**354-404 pgs. 297-305**

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• **The NIH should support efforts to develop novel and rapid methodologies for the detection and identification of opportunistic pathogens in HIV-infected persons.**	Opportunistic Infections Research pg. 35	**416 pg. 316**	**354-404 pgs. 297-305**
• **Regarding specific pathogens, the following issues should be addressed: KSHV—drug susceptibility, efficacy of foscarnet as therapy for KSHV infection; *B. henselae*–antibiotic efficacy in cat scratch disease versus bacillary angiomatosis, appropriate duration of therapy.**	Opportunistic Infections Research pg. 35	**417 pg. 316**	**354-404 pgs. 297-305**