NIH AIDS Research Program Evaluation

NATURAL HISTORY, EPIDEMIOLOGY, AND PREVENTION RESEARCH AREA REVIEW PANEL

Findings and Recommendations

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Table of Contents

Executive Summary 1

Introduction 5

I. Panel Methods of Review and Descriptive Statistics 11

II. Scientific Priorities and Recommendations 14

A. Sexual Transmission Subpanel Report 14
B. Perinatal/Postnatal Transmission Subpanel Report 15
C. Parenteral/Injection Drug Use Transmission Subpanel Report 17
D. Natural History/Disease Progression Subpanel Report 19
E. Methodology Subpanel Report 22

III. Review of Natural History, Epidemiology, and Biomedical Prevention Research at the National Institutes of Health by Scientific Priorities 24

IV. Review of Natural History, Epidemiology, and Biomedical Prevention Research at the National Institutes of Health by Institute and Center 25

A. National Institute of Allergy and Infectious Diseases 25
B. National Heart, Lung, and Blood Institute 28
C. National Institute of Child Health and Human Development 29
D. National Institute on Drug Abuse 30
E. National Cancer Institute 32
F. National Institute of Mental Health 33
G. Fogarty International Center 35
H. Other Institutes and Centers 36

V. Special Issues 37

A. Funding Mechanisms 37
B. Peer Review 39
C. Cross-Institute and Interagency Collaborations 39
D. Cross-Disciplinary Research: Overlap With Other Panels 40
E. Links Among Research, Services, and Communities 40
F. Links Between the Public and Private Sectors 41
G. Access and Ownership of the Products of NIH-supported AIDS Research 42

VI. Conclusions and Recommendations 43

Appendixes

A. Biographies of Panel Members
B. Acknowledgments

Executive Summary

The scientific foundation for HIV prevention programs is provided by natural history, epidemiology, and biomedical prevention research, together with social, behavioral, and vaccine research. Epidemiologic studies have been defining the scope of the epidemic, determinants of transmission, and the course and determinants of disease progression. Carefully designed longitudinal studies now provide the essential "laboratory" for clinical research of the virology, immunology, and pathogenesis of HIV infection. Recent advances in these basic sciences and the rapid changes in the nature of the global pandemic now dictate an emphasis on new areas that range from molecular epidemiology (including the transmission and natural history of infection with different viral subtypes) to social and ecological epidemiology (including the influence of ecological factors and social networks on HIV transmission) to definitive biomedical intervention trials.

Epidemiologic studies have defined a rapidly growing number of potential biomedical interventions for preventing transmission of HIV and sequelae of HIV infection. For example, among many potential biomedical interventions for preventing sexual transmission of HIV are the use of various spermicidal and nonspermicidal topical microbicides; the early recognition and treatment of several sexually transmitted diseases (STDs), such as syphilis, chancroid, genital herpes, gonorrhea, chlamydial infection, and trichomoniasis; and the use of mechanical barriers. Potential interventions to prevent perinatal or postnatal transmission include low-cost approaches such as avoidance or shortened duration of breast-feeding, intrapartum vaginal cleansing, and vitamin supplementation as well as higher cost approaches such as evaluation of antiretroviral combinations for prophylaxis. Interventions for preventing parenteral transmission by injection drug use (IDU) can be developed and evaluated and will involve such basic steps as developing practical and effective approaches to syringe/needle sterilization and the impact of enhancing needle-exchange programs. Potential biomedical interventions that may reduce transmission by any route include early detection and treatment of primary HIV infection and postexposure chemoprophylaxis. Many of these biomedical interventions are as promising as many behavioral interventions; therefore, future multicomponent intervention trials to prevent HIV transmission should include both biomedical and behavioral interventions. The remarkable progress in prevention research during the past few years and the number of additional biomedical interventions now urgently requiring evaluation make this one of the most promising areas of HIV research today and one of the strongest sources of optimism in combating the HIV pandemic. Whereas pharmaceutical research is largely funded by industry, prevention research is the responsibility of the public sector. Nonvaccine biomedical prevention research is, therefore, a high priority for NIH AIDS research, yet it receives less than 1 percent of the total NIH AIDS research budget.

HIV Prevention Research Overview

The development and testing of preventive interventions must be a well-planned process that begins with definition of the points of attack through epidemiologic research and proceeds systematically through development of an intervention and careful testing of the intervention in a sequential process. Much like clinical trials of new pharmaceuticals, these interventions must be planned and evaluated with the most rigorous study designs possible. The planning, conduct,

and analysis of prevention trials must be interdisciplinary, whether the trial involves a single biomedical or sociobehavioral intervention or a combination of biomedical and sociobehavioral interventions. It is important that national and international efforts in prevention science be well coordinated and that findings from prevention research be translated as quickly as possible into effective prevention services. The Panel developed a series of crosscutting recommendations to address some of the critical work needed in this area.

Recommendations

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

   Key components of this strategy include social and behavioral approaches as well as the biomedical (including vaccine) approaches to prevention. The strategy should coordinate these three approaches across Institutes; be comprehensive, addressing the most promising methods for preventing sexual, parenteral, and perinatal transmission; and be coherent, involving systematic progression through a series of phases leading to intervention trials. To ensure an orderly sequence of prevention studies, randomized trials will require methodologic guidelines analogous to the trial-phasing system used in clinical trials of therapeutic agents, from the identification of potentially modifiable risk factors for HIV transmission to the identification and evaluation of interventions to interrupt transmission. Rigorous study designs are essential in HIV prevention trials, which may require levels of funding comparable to those used in clinical trials of pharmaceuticals. The NIH should provide appropriate levels of support for definitive prevention research.

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.**

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.**

Determinants and Prevention of HIV Transmission

Epidemiologic research on prevention of HIV transmission initially requires identification of determinants of sexual, perinatal, postnatal, and parenteral transmission. Epidemiologic HIV/AIDS research, like other fields of HIV/AIDS research, is a dynamic, interactive process. Modifiable risk factors vary in different populations and places and can change over time. The development of improved research tools from laboratory, clinical, and social and behavioral science continuously allows epidemiologists to address new questions and use new approaches

to old questions. Ultimately, factors that are found to be common or to greatly facilitate HIV transmission form the targets for coordinated biomedical and sociobehavioral interventions. Many such targets have been identified and must be urgently addressed in prevention trials.

Many opportunities exist for synergistic interdisciplinary research on determinants and prevention of HIV transmission. Expertise in social and behavioral research should routinely be a part of research on biomedical interventions. For example, qualitative social research and sociobehavioral expertise should be utilized in trials evaluating the use of topical microbicides, studies of the duration of breast-feeding of infants at risk, improvements in access to needle/syringe-exchange programs, and recognition and treatment of STDs, including postexposure prophylaxis. Conversely, social and behavioral trials and evaluations should include expertise in biomedical research.

Opportunities also exist within therapy and vaccine trials to include intermediate markers that are very important for research on HIV transmission. Therapy trials, which primarily address individual benefit, also could address the potential for public health benefit by measuring the impact of therapy on mucosal shedding and transmission of HIV. Future vaccine trials also could examine the impact of vaccines on subsequent HIV shedding and transmission by vaccinated persons who develop "breakthrough" infection. These opportunities must not be wasted. However, *ad hoc* prevention research retrofitted to studies designed for other purposes is no substitute for the *de novo* directed prevention research called for above.

Recommendations

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.**

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.**

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

Natural History and Disease Progression

Well-designed studies of the natural history of HIV infection are elucidating mechanisms of disease progression and have become essential to basic research on pathogenesis of human HIV infection. Many preventive and therapeutic interventions, such as primary prophylaxis for *Pneumocystis carinii* and *Mycobacterium avium* complex and secondary prophylaxis for invasive fungal infections and toxoplasmosis, are based on these studies.

By closely linking ongoing natural history studies to basic virologic and immunologic research, new insights will be gained in targeting populations at risk for specific HIV-related outcomes and in developing new strategies for preventive and therapeutic interventions. Development of cohorts of individuals with newly acquired, early HIV infection is particularly important. Such cohorts can be population based (arising from existing high-risk uninfected cohorts) or based on referral of newly infected persons. Inclusion of virologists and immunologists in research involving new cohorts of persons with early HIV infection will lead to better understanding of how immunologic and virologic events of early HIV infection influence subsequent disease progression. These studies also are critical to developing successful strategies for identifying persons with primary HIV infection and evaluating the role of early therapeutic intervention in interrupting the replication cycle and delaying the course of disease progression.

Recommendations

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.**

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.**

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.**

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.**

Introduction

The charge to the Panel was to review natural history, epidemiology, and biomedical prevention (NHEBP) research; evaluate the effectiveness and appropriateness of current and planned research programs in this area; formulate recommendations; and set priorities for the future NHEBP research. A part of this charge was to offer guidance on how prevention science objectives can be better achieved by identifying new research needs and opportunities, expediting the bureaucratic process, streamlining lines of authority, establishing liaisons between research centers, and addressing the cost-effectiveness of recommendations. To these ends, the Panel also considered relevant methodologic issues for such research; evaluated current program effectiveness and design; determined what new programs and approaches to research on prevention, transmission, and natural history of HIV infection should be developed and added to existing programs and approaches; set priorities based on the effectiveness of programs and approaches; and examined earlier budget recommendations.

The Panel was organized into five subpanels: Sexual Transmission; Perinatal/Postnatal Transmission; Parenteral/Injection Drug Use Transmission; Natural History/Disease Progression; and Methodology. Each of these subpanels evaluated both nonintervention research and intervention/prevention trials relevant to the subpanel areas of interest. The objectives of each subpanel were to define what is known, what is in progress, and what needs to be known. The subpanels assigned research priorities according to the magnitude and severity of the problem addressed; amenability to research with existing techniques; implementability; and uniqueness of approach. Overall, the focus of attention in the prevention area was limited to biomedical modalities; however, the Panel established crossrepresentation with the Behavioral and Social Sciences Area Review Panel to address areas of common interest, such as sexual networks and ecologic studies. Other links were established with the Panels on Vaccines, Etiology/Pathogenesis, and Clinical Trials.

Overview of Study Designs and Analysis Strategies in Epidemiology

Prevention Science

Prevention science is multidisciplinary, encompassing epidemiology as well as social and behavioral sciences, communication science, clinical medicine, biostatistics, health services research economics, and laboratory science. The public sector plays a vital role in prevention science, given the relative dearth of a prevention constituency in the private sector or within affected communities.

Epidemiology

Observational epidemiologic research includes both descriptive and analytic studies. Descriptive studies define the frequency and pattern of distribution and natural history of disease in populations. Analytic epidemiological methods, including case-control studies and prospective followup studies, help to define risk factors for HIV transmission or progression. Risk factors may operate at an individual or a population level (e.g., social networks and ecological conditions that may influence the acquisition of HIV). Molecular epidemiology

refers to the synergistic combination of basic science and epidemiology, which is one of the most rapidly growing areas of epidemiology. For example, research in this area can focus on the individual level and investigate the potential role of T-cell receptor variation in HIV susceptibility, or it can focus on the population level and investigate the influence of viral subtype on the pattern of HIV distribution in different populations.

Policy implications can be directly forthcoming from observational studies, as can guidance for future public health as well as basic science research. For instance, safer sex messages were derived directly from the earliest epidemiologic studies. The recommendations regarding access to sterile needles and drug abuse treatment were derived from the first descriptive studies of users of injection equipment, such as persons who were observed to have a reduced risk of HIV infection because they were diabetics with access to needles and syringes. In addition, the appreciation of the diversity of patterns of clinical progression (e.g., rapid progressors, long-term survivors) emerged from observational cohort studies.

Within observational studies, existing unusual circumstances can frame "natural experiments" so that unanticipated events provide valuable insights. Examples of observational studies that yielded unexpected insights include the study of transfusion recipients in Australia that led to the molecular epidemiologic definition of *nef*-deletion; the study of repeatedly exposed commercial sex workers in Africa that showed some women remaining uninfected; and studies of pregnant mothers that elucidated the circumstances of maternal/fetal transmission. Also, observational cohorts that identified long-term survivors and other persons with unusual outcomes (e.g., stable low CD4 counts without clinical disease) have provided a focus for studies of possible correlates of protection from disease.

Although the results of observational epidemiologic studies *per se* may warrant health promotion/disease prevention policy change, observational studies that identify potentially modifiable risk factors for HIV transmission or progression should lead, where feasible, to the next phase of prevention research: the experimental preventive intervention trial, a form of interdisciplinary research in which epidemiologists continue to play an important role. Such trials introduce a specific intervention designed to modify a putative risk factor and evaluate the impact of the intervention on transmission or progression of HIV.

Table 1 summarizes a large number of potential interventions that warrant further study for prevention of HIV transmission. These interventions are divided into four groups, according to route of transmission (sexual, parenteral, perinatal/postnatal, or any route). Within each group, potential interventions are listed, beginning with those with primarily social or behavioral objectives and proceeding to interventions that are increasingly biomedical but, nonetheless, require behavioral components. Most of the listed categories of interventions actually incorporate a broad class of interventions, each having many possible subcategories and a number of different target populations. For example, interventions to reduce HIV transmission include a number of interventions for different STDs that have been associated with HIV transmission, such as genital ulcers, gonorrhea, chlamydia, and trichomoniasis. The prevalence of these STDs varies in different populations, and there are many different approaches to controlling each of them. Many types of topical microbicides are of interest, and they can be used by both heterosexual and homosexual men and women. Many antiretroviral drugs are of

interest in preventing perinatal transmission, and a range of durations of breast-feeding should be assessed in trials to prevent postnatal transmission. The design, implementation, and evaluation of interventions in certain subpopulations, such as adolescents, may require separate intervention trials.

Social and behavioral intervention research has been supported by NIH for some time. However, until recently, remarkably few of the biomedical interventions have been the focus of intervention research supported by any of the NIH Institutes, Centers, and Divisions (ICDs), and many potentially important interventions have not been studied at all despite very persuasive observational epidemiologic data identifying a number of risk factors as potential targets for biomedical interventions. Thus, there is a large backlog of biomedical intervention research that urgently requires attention. Some of these interventions may require additional study before formal evaluation in intervention trials, and some may not be appropriate for randomized controlled trials (RCTs). Ultimately, preventive intervention trials may be designed as RCTs or as quasi-experiments.

It is increasingly evident that preventive intervention trials logically should involve a series of steps, or phases, which can be viewed as analogous to the trial-phasing system used in clinical trials of pharmaceutical drugs (Table 2). It is essential that investigators, funding agencies, research ethicists, policymakers, and the public understand the actual stage of development that has been achieved, and that which is still needed, in the development of effective interventions.

Table 1. Potential approaches to sociobehavioral and biomedical interventions to reduce HIV transmission*

Sexual Transmission	**Parenteral Transmission - IDU**
Delay onset of sexual activity	Prevent initiation into IDU
Have fewer partners	Avoid sharing injection equipment
Use safer sexual practices	Avoid risky injection practices
Choose safer partners, safer sexual networks	Treat drug use and alcoholism - abstinence - harm reduction
Promote early recognition and treatment of STDs	
Use topical microbicides	Promote needle/syringe sterilization
Assess use of postcoital and menstrual hygiene	Promote needle-exchange enhancements
Assess use of mechanical barriers: condoms, diaphragms	
Assess risk of hormonal contraceptives in the absence of use of effective barriers	
Normalize vaginal flora	
Treat cervical ectopy	
Assess role of male circumcision	
Perinatal/Postnatal Transmission	**General - Transmission by Any Route**
Increase counseling on reproductive decision-making	Modify social environments, risk networks
Avoid or abbreviate breast-feeding	Develop HIV vaccines
Assess use of vaginal cleansing intrapartum	Use antiretroviral treatment of HIV-infected persons, including early detection and intervention in persons with HIV infection
Assess use of vitamin A therapy	
Assess use of HIV immune globulin perinatally	Increase prevention/management of OIs and other cofactors to reduce HIV replication, shedding
Assess role of cesarean section	
Use antiretroviral therapy	Assess use of postexposure chemoprophylaxis

*These suggestions for interventions are at various stages of research, with some ready to go into RCTs and some still requiring hypothesis testing.

Table 2. Parallels between the concepts of "phasing" used in pharmaceutical research and possible phasing of research on sociobehavioral and biomedical interventions for prevention of HIV infection

Phase	Pharmaceutical Research	Prevention Research
Pre-Phase I (discovery)	• Chemistry, microbiology, toxicology • Activity, toxicity *in vitro*, in animals	• Drugs and biological products (e.g., microbicides): same as pharmaceuticals • Define risk factors or correlates of protection: descriptive epidemiology • Formative behavioral studies
Phase I (small)	• Safety in dose-ranging studies • Pharmacokinetics • Low-risk participants	• Drugs and biologicals: same as pharmaceuticals • Safety, acceptability, feasibility of interventions • Analytic epidemiologic hypothesis testing (e.g., case-control study) • Low-risk participants
Phase II (intermediate size)	• Safety in high-risk participants (i.e., HIV-infected) • *In vivo* biologic activity • Surrogate markers as endpoints (e.g., CD4, viral load) • Randomized or nonrandomized (i.e., time-series/historical control) • Concurrent open access/parallel track	• Safety in high-risk participants (i.e., high risk of acquiring HIV) • *In vivo* activity of drugs, biologicals • Surrogate markers as endpoints (e.g., self-reported behavior change or condom use; other STDs as surrogates for HIV infection) • Analytic epidemiologic hypothesis testing (e.g., cohort study) • Randomized or nonrandomized (i.e., time-series/historical control; ecologic comparisons with other communities) • Concurrent implementation if feasible
Phase III (large) Efficacy trial: the critical trial that would clearly establish the risk/benefit ratio	• Primary endpoints: clinical morbidity, mortality, quality of life • Large RCT	• Primary endpoints: HIV infection; morbidity and mortality in those who become infected; secondary transmission • Large RCT - Community randomization - Individual randomization
Phase IV (post-marketing or post-implementation)	• Extension of proof of efficacy in some important refinement, such as dosing, duration of effect with longer followup, combination therapy, new indications • Long-term safety, rare toxicities • May involve both RCT and surveillance	• Effectiveness at population level (e.g., efficacy x% reached x% compliance) • Impact of type of population reached (core vs. noncore) • Cost-effectiveness or cost-utility at population level • Important refinement (e.g., randomize continuation beyond 1 year) • Possible long-term or rare adverse effects

Randomized Controlled Trials in Prevention Research

An RCT should be considered the most definitive test of the efficacy of a preventive intervention. Criteria for when an RCT is the most appropriate design are discussed below, in section E, Methodology Subpanel Report. The role of RCTs is crucial in evaluation of the effect of new drugs on HIV disease progression. Within HIV prevention, vaccine trials are another example of the appropriate use of RCT design. Many social and behavioral science trials are in progress to gain insights on the most effective sociobehavioral change strategies.

However, the literature contains few reports of RCTs that have used HIV prevention as an endpoint. This contrasts sharply with the large number of RCTs that have used HIV disease progression as an endpoint. Despite the relatively small investment in RCTs evaluating biomedical intervention to prevent HIV transmission, the yield has been remarkably great. For instance, a trial sponsored by the AIDS Clinical Trial Group (ACTG 076) dramatically and convincingly demonstrated the efficacy of AZT in preventing perinatal HIV transmission, and a trial sponsored by the European Community showed that controlling symptomatic STDs is quite effective in reducing incidence of HIV infections. Such trials have provided a basis for optimism and action in combating the HIV pandemic.

The number of RCTs of novel prevention strategies has been far below the scientific need and inconsistent with the demonstrated benefits of this type of research. Existing vaccine, drug treatment, or behavior RCT programs have not adequately pursued the many compelling avenues for the development of effective interventions for the biomedical prevention of HIV transmission. An urgent need exists for RCTs to evaluate the use of topical microbicides, novel female-controlled barriers, perinatal topical antisepsis, and nutritional supplementation. Other critical trials should be developed to determine the most effective and feasible STD control strategies, identify the most effective low-cost antiviral strategies for reducing perinatal transmission, determine the optimal duration of breast-feeding, assess the impact of postcoital and menstrual hygiene practices, and determine the best means for providing sterile needles and syringes. Furthermore, there is an urgent need for RCTs of multicomponent interventions that employ both biomedical and behavioral interventions, e.g., interventions that employ condom promotion plus early recognition and treatment of STDs in adolescents. These novel technologies and HIV biomedical prevention strategies are within the purview of this Panel.

Quasi-Experiments

The quasi-experiment is a technique to create a legitimate and valid research paradigm around a real-world circumstance. If randomization and blinding are neither ethical nor feasible, creative research methods can yield inferences as to the likely impact of a given intervention. Unlike RCTs, which have randomly selected, concurrent, and comparable intervention and control groups, quasi-experiments use nonequivalent control groups or time-series designs. For instance, the correlation of commercial sex work and condom utilization with diminished HIV risk was first noted within a quasi-experiment.

I. Panel Methods of Review and Descriptive Statistics

The Panel solicited testimony and written documentation from diverse sources. ICDs with major research portfolios in natural history and epidemiology were invited to a Panel meeting to briefly present their programs, engendering a dialogue about the accomplishments, gaps, and future directions of their portfolios. Specific questions were sent to the ICDs in advance of the meeting; examples of questions included the following: What have been your best projects/programs with respect to science and mechanisms of support? What new initiatives have been proposed this year? How do they relate to existing programs and areas of emphasis? What are the implications of growth in the program? How might the OAR facilitate research goals and plans? All ICDs were contacted by the OAR and asked to provide detailed information on each area of interest.

Program staff from the Centers for Disease Control and Prevention (CDC) were invited to attend Panel meetings as *ad hoc* members to provide information on areas of overlap and opportunities for collaboration/coordination with the CDC programs in natural history and epidemiology. A Panel session was devoted to discussions with key CDC staff working in areas complementary to those of interest to the Panel.

A meeting also was held in conjunction with an international STD/HIV meeting, affording the opportunity for active dialogue with investigators working in all areas of the world particularly affected by HIV disease. This Panel meeting specifically facilitated a review of research conducted in other countries on STD treatment approaches for preventing sexual transmission of HIV, research on additional approaches to prevent sexual transmission, HIV/STD biomedical prevention research at the CDC, observational research and prevention trials on perinatal/postnatal transmission of HIV, nonintervention research and prevention trials on parenteral/IDU transmission, and nonintervention and prevention research on natural history and disease progression.

An open meeting was held to allow for public testimony and comments. This meeting was advertised in the *Federal Register* and posted on several electronic bulletin boards. In addition, more than 130 community-based organizations, professional organizations, members of community advisory boards, funded investigators, and HIV-infected persons received personal notification of the meeting by mail, fax, or personal phone call. Despite the advance notice, only four oral presentations were made at the meeting (two on needle exchange/harm reduction and two on the status of funded cohort studies).

The Panel used the available NIH databases, including the OAR AIDS Research Information System (ARIS) and the Division of Research Grants database of abstracts from funded projects, the Computer Retrieval of Information on Scientific Projects (CRISP) database. The awards in the Panel's area of emphasis were summarized in ARIS reports that allowed the Panel to scrutinize this research according to the funding ICD, total funds allocated, percentage of funds from AIDS dollars, site/investigator, funding mechanism, and the 1994 Strategic Plan Objective. Award numbers were linked with the CRISP database so that abstracts (as written by the principal investigator at the time of grant submission) could be reviewed.

The budget figures given in this Panel report were derived from allocations of research funds, determined in accordance with the NIH Strategic Plan for HIV-Related Research that is developed each fiscal year (FY) by the OAR, the ICDs, and the Coordinating Committees. The total NIH funding attributed by NIH to the area of NHEBP research in FY 1994 was reported by the ICDs to be $180,603,603 (See Table 3). The ICDs contributing the most funding to research on the epidemiology and natural history of HIV/AIDS are:

- National Institute of Allergy and Infectious Diseases (NIAID, $66,573,850)
- National Heart, Lung, and Blood Institute (NHLBI, $35,311,638)
- National Institute of Child Health and Human Development (NICHD, $17,048,263)
- National Institute on Drug Abuse (NIDA, $16,036,704)
- National Cancer Institute (NCI, $14,728,011)
- National Institute of Mental Health (NIMH, $11,975,424)

These six ICDs account for 90 percent of the total funding available for research on the natural history and epidemiology of HIV/AIDS.

These dollars were expended in FY 1994 according to four research objectives identified in the NIH Five-Year Plan for HIV-Related Research:

- Objective 1A, Epidemiology of HIV in Special Populations (142 awards, $35,713,359)
- Objective 1B, Natural History of HIV in Special Populations (497 awards, $91,319,213)
- Objective 1C, Natural History of HIV in Pregnant Women (146 awards, $30,973,761)
- Objective 1D, Blood Safety/Supply (56 awards, $22,597,270)

The Panel found that assessing the research according to allocations within the objectives was not useful to the review process because of inconsistencies among the criteria used by different ICDs to assign research to one objective versus another.

In FY 1994, a total of 841 awards were made, comprising more than 2,000 separate subprojects. Extramurally funded research in epidemiology and natural history accounted for 96 percent of the dollars and 98 percent of the total 841 awards. A large proportion of extramural research in this area of emphasis is funded using “directed” mechanisms of funding: cooperative agreements (U01s) accounted for 18 percent of the $180,603,603 expended and 32 percent of the number of awards made; contract mechanisms (N01s) accounted for 24 percent of the funds and 12 percent of the awards. Unsolicited, investigator-initiated (R01) awards accounted for 34 percent of the total funds and 26 percent of the awards. There were 41 training awards (5 percent of awards) funded in FY 1994 totalling $3.6 million (2 percent of $180 million), or about $88,000 total costs per traineeship in that year. The remaining funds in NHEBP research were expended using other award mechanisms.

Table 3. Distribution of Resources Available for Natural History, Epidemiology, and Prevention Research, by ICD for Fiscal Year 1994

	Expenditure	Percent of Total
NIAID	$66,573,850	36.9
NHLBI	35,311,638	19.6
NICHD	17,048,263	9.4
NIDA	16,036,704	8.9
NCI	14,728,011	8.2
NIMH	11,975,424	6.6
NCRR	4,651,585	2.6
OD	3,635,917	2.0
NIDR	3,364,236	0.2
NINDS	2,517,019	0.1
NIDDK	2,294,599	0.1
NIAAA	1,420,505	0.1
NIAMS	366,674	*
NINR	346,139	*
NIDCD	333,039	*
FIC	0	0
NIA	0	0
NIEHS	0	0
NCGHR	0	0
NEI	0	0
TOTAL	$180,603,603	100.00

* Totals less than 0.1 percent.

II. Scientific Priorities and Recommendations

A. Sexual Transmission Subpanel Report

The occurrence of HIV is influenced by the prevalence of a variety of factors related to social, behavioral, and ecologic influences, to host susceptibility, and to infectiousness. At the level of a whole population, the prevalence of HIV infection depends on demographic influences, social norms, and access to care for such conditions as drug and alcohol use and STDs. In particular, treatment of symptomatic STDs in certain populations has reduced sexual transmission of HIV. When social, behavioral, and ecologic risk converge—as in gay runaway youth or high-risk heterosexual adolescents—the impact on HIV transmission is compounded. Host susceptibility to HIV infection is associated with sexual and contraceptive practices; factors relevant to genital anatomy/physiology including male circumcision and cervical ectopy; vaginal flora and douching or other hygienic practices; and immunological factors, genetic factors, and other biologic conditions such as concurrent infections. For example, for heterosexual transmission, evidence exists that susceptibility to HIV infection increases with lack of male circumcision, increased cervical ectopy in adolescent and young women, depletion of hydrogen-peroxide-producing vaginal lactobacilli, and/or increased vaginal pH. Decreased susceptibility to HIV infection has been associated with specific Human Leukocyte Antigen (HLA) types. Similarly, homosexual transmission has been particularly linked to receptive anal intercourse and compromised integrity of the rectal mucosa.

Infectiousness varies as a function of stage of infection, genital shedding, and viremia. Infectiousness also may be influenced by viral clade and by the pattern of quasi-species found in the genital tract. Viremia and genital shedding of HIV appear to be at the highest levels early in the course of infection but are intermittent and occur throughout the natural history of HIV infection. They are also influenced by such factors as antiviral treatment, and genital shedding is influenced by coinfection with STDs.

Scientific Opportunities

Advances in identifying socioecologic influences on HIV prevalence have expanded the focus of research from “risk groups” to the determinants of specific partner-selection practices and identification of routes of spread from infected to uninfected subgroups. This has led to a new emphasis on the study of “sexual networks.” The prevalence of STDs in these networks has been shown to make an important contribution to risk of HIV transmission. This underscores the importance of a renewed focus on STD control, specifically the importance of developing rapid, inexpensive STD diagnostic tests that could facilitate STD diagnosis among individuals who avoid traditional clinic settings or who live in resource-poor areas.

Strong evidence supports the protective effect of male condoms against transmission of HIV when used consistently and correctly. In contrast, the effects of hormonal methods of contraception and spermicides on susceptibility to HIV infection are unclear, underscoring the need for additional, carefully designed studies of these and other approaches to contraception that are linked with HIV prevention. Specific studies are needed to address issues of biological effects as well as behavioral factors such as acceptability of various barrier contraceptives.

Increasing scientific understanding regarding other factors that may influence susceptibility (e.g., immune function; parasitic infections; malnutrition; and sexual and hygienic practices, such as douching and use of vaginal desiccants; female circumcision; and cervical ectopy) emphasizes the need for culturally specific prevention research targeting these factors. Such research requires unique resources, since highly developed community and interdisciplinary professional expertise is necessary to ensure recruitment and retention of high-risk persons, including youth, active drug users, and minorities.

Methods that can decrease infectiousness also are essential to controlling the HIV epidemic. The progress that is being made in developing new measures of viremia provides opportunities for research on the impact of systemic antiretroviral therapy and topical microbicides on cervical and rectal shedding of HIV as well as on HIV transmission. Similarly, the new tools of molecular epidemiology should be applied to studies of increased viral infectiousness during the primary stage of infection with various viral clades. Treatment of gonococcal urethritis in men significantly reduces urethral shedding of cell-associated HIV in infected men. The significance of curing various STDs on genital shedding of cell-associated and cell-free HIV in men and women requires much more study.

Recommendations

II.A.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.

II.A.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.

II.A.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.

II.A.4. Develop rapid, inexpensive, and simpler diagnostic tests for STDs to facilitate treatment, thereby strengthening prevention and control of HIV and STDs.

B. Perinatal/Postnatal Transmission Subpanel Report

The ACTG 076 trial demonstrated the efficacy of antiretroviral treatment in reducing maternal-fetal transmission of HIV. Compelling data suggest that reduced viral exposure during pregnancy and birth might reduce perinatal HIV transmission. For instance, the possible preventive efficacy of cesarean section suggests that reduced perinatal viral exposure may

reduce vertical transmission. Breast-feeding also has been associated with vertical transmission of HIV.

Scientific Opportunities

The above findings leave many unanswered questions. Nothing is known about the efficacy of zidovudine (AZT) in pregnant women with CD4+ cell counts below 200/μl or in those with a history of prior AZT treatment; the most effective antiviral drug(s); or the optimal timing of therapy. The role of short-course antiretroviral therapy in the prevention of perinatal transmission also must be explored in high-prevalence, resource-poor countries. Other possible approaches to preventing mother-fetal transmission include use of potential vaccines, hyperimmune globulin, or other chemotherapies, alone or in combination. Low-cost interventions, such as vitamin supplementation and vaginal cleansing, also need to be explored.

In addition to early cesarean sections, other approaches to delivery that induce less trauma and hemorrhage might reduce perinatal HIV transmission. Intrapartum vaginal washing and infant antiseptic cleansing are among the alternatives that should be investigated further. Negative findings from a single study should stimulate efforts to follow an orderly, systematic plan to develop and evaluate products and strategies toward this important objective.

Although researchers have associated breast-feeding with vertical transmission of HIV, additional information is needed to develop effective prevention strategies. Specifically, there is a pressing need to determine how the duration of breast-feeding, the mother's stage of illness, and her level of viremia (singly and in combination) affect the transmissibility of HIV. Related research is needed to evaluate the safety, effectiveness, and acceptability of alternatives to breast-feeding such as formula feeding and surrogate feeding by HIV-uninfected women.

Long-term followup of children born to HIV-infected mothers should be included as part of current, ongoing perinatal transmission studies. This followup research is needed to study the influence of viral and host factors and the timing of transmission on the spectrum of disease. Such research should include efforts to assess the effects of exposures to HIV-related infections on growth, development, and behavioral factors in offspring**.** In addition, the possible changing patterns of natural history due to the evolution of clinical management need to be explored. For example, long-term survivors with perinatally and postnatally acquired infection should continue to be followed to assess which factors are important in viral suppression and in a vigorous host immune response. Antiretroviral-exposed uninfected infants born to HIV-infected women provide an opportunity to assess whether there are any untoward long-term side effects of antiretroviral exposure *in utero*.

Continued long-term followup of HIV-infected mothers also is needed. Many questions remain about HIV infection and health care management during pregnancy. Optimal strategies for prevention and treatment of OIs in pregnancy, such as maximally effective prophylaxis regimens for *Pneumocystis carinii* pneumonia (PCP) and cervical dysplasia, need to be determined. Little is known about factors that may affect the decisions of HIV-infected women to bear children, such as the availability of antiretroviral therapy to reduce vertical HIV

transmission, counseling by health care workers, demographic and cultural factors, sexual orientation, method of conception, and mode of acquisition of HIV.

Recommendations

II.B.1. Develop modalities to minimize perinatal transmission that extend benefits of chemoprophylaxis, including hyperimmune globulin and combination chemotherapies.

II.B.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.

II.B.3. Design and test behavioral and social intervention strategies specifically for HIV-infected, pregnant women regarding therapies to reduce vertical HIV transmission.

II.B.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.

C. Parenteral/Injection Drug Use Transmission Subpanel Report

In the United States, IDUs constitute the second largest group of persons infected with HIV. Studies of IDUs are important, not only because of the high prevalence of HIV infection among this population, but also because IDUs constitute an important conduit of infection to other risk groups. A large portion of the heterosexual epidemic and most of the pediatric epidemic in this country are attributed to transmission from IDUs who often have sexual partners who do not inject drugs. Likewise, the importance of crack cocaine in contributing to the spread of the epidemic may be attributed to the fact that crack users, who are known to exchange sex for drugs, are likely to have had infected IDUs among their sexual partners. Men who both inject drugs and have sex with men are more likely to be infected than other drug users, contributing to the continuing epidemic among men who have sex with men. Parenteral IDU accounts for a portion of the HIV infection among women who have sex with other women. The roles of early alcohol and drug experimentation among adolescents and the social networks that foster drug use in youth are especially important factors in prevention research.

Many of the specific behaviors that can transmit HIV among IDUs are well understood. Sharing of syringes and needles transmits HIV, and locations such as shooting galleries are places where multiple users sharing needles spread HIV from one to another. The evidence is convincing that needle/syringe exchange can contribute significantly to prevention efforts: this exchange is associated with lower rates of transmission of HIV, as well as with lower rates of other infectious diseases that can be surrogates for HIV, such as hepatitis B and hepatitis C.

Scientific Opportunities

Now that needle-exchange programs have been judged successful, renewed attention should be given to those programs with a focus on the best ways to facilitate access to sterile syringes. Specific attention should be given to ways of attracting and retaining users and ways of collecting used needles and syringes. In addition, the impact of laws, police practices, and pharmacy retail sales of syringes and needles should be investigated within the context of the NIH AIDS research mission to inform policy decisions about sterile syringes and needles.

Even though risk factors for infection among IDUs have been identified, the varying distribution of infection among IDUs throughout the country cannot be explained simply by the varying prevalence of such factors. Given the same needle-sharing behaviors, infection rates vary depending on ecologic factors defined by demographic, social, and cultural variables. African-American or Puerto-Rican IDUs are more likely to be infected than other racial and ethnic groups. Similarly, areas in the Northeast have large-scale epidemics among IDUs, whereas areas in other parts of the country that show a similar array of risk behaviors do not have the same problem. The contribution of these ecologic factors, as well as selection of needle-sharing partners on an individual level, must be considered. These same kinds of factors also are likely to influence initiation into IDU and non-IDU behaviors as well as influence the use of particular drugs, including crack cocaine. Exploration of these ecologic and "social network" factors also can yield information about behaviors associated with drug dependency so that drug or antiretroviral treatment issues can be addressed simultaneously with studies aimed at reducing HIV transmission.

Although the importance of IDUs in contributing to transmission of HIV to non-IDUs has been well established, the direct influence of IDU on transmission has not been well characterized. Using the tools of molecular epidemiology, research can now focus more directly on transmission issues such as the interaction of drugs and injecting behaviors on viral type, viral load, or shedding. Results from these studies also can be applied to research on the natural history of HIV infection among HIV-infected IDUs in order to determine whether factors related to route of administration of drugs or the types of drugs used can influence disease course. Applied laboratory studies now clearly must address the survival and transmissibility of HIV on IDU equipment. Sterile syringes and needles prevent transmission but they are not always available. Bleach is not as effective a decontaminating agent as was originally hoped. The manner in which bleach is used, including compliance with current bleach-use guidelines, must be investigated. Other agents that can decontaminate syringes and other drug paraphernalia also should be explored. As a prerequisite to these studies, research must continue to focus on methods to study the survival of HIV on such equipment.

Recommendations

II.C.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.

II.C.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.

II.C.3. Investigate interactions of IDU and IDU-related behaviors on viral load, viral subtype, and viral shedding.

II.C.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.

D. Natural History/Disease Progression Subpanel Report

Investigation of the natural history of HIV infection is critical to the elucidation of the mechanisms of infection and disease progression and to the application of this knowledge in targeting appropriate preventive and therapeutic interventions. A number of natural history studies indicate that the overall course of HIV disease progression in developed countries is very similar among demographically diverse groups, given equal access to care. There are, however, known differences in risk of specific OIs by gender, risk group, and geographic region that guide effective clinical interventions and serve as an impetus to search for cofactors of disease progression. The only clearly documented cofactor associated with more rapid progression to AIDS in adults is increasing age at seroconversion. CD4 lymphocyte count has been the most widely used and best single predictor of outcome to date, although new data indicate that plasma viral load may be a more stable measurement that is more closely linked with clinical outcome. Clinical findings such as clinical symptoms and signs and OIs may be additional markers of more rapid progression.

Cohort studies have produced important insights into disease progression by describing subgroups of HIV-infected or exposed persons with “uncommon outcomes,” including rapid progressors, nonprogressors, persons with low CD4 counts without clinical disease, and HIV-exposed uninfected persons. These studies have begun to identify virologic, immunologic, and genetic characteristics of individuals in these unique subgroups that may ultimately be useful for targeting intervention research. In addition, selected populations, such as exposed infants, pregnant women, adolescents, and persons with novel coinfections, are inherently of interest because of their unique exposures or biological or social characteristics.

Most studies of the natural history of HIV infection have enrolled individuals well after the time of infection. However, recent evidence suggests that events early in infection as well as early stages of therapeutic intervention may determine the course of HIV disease progression. In addition, newly infected persons may be at increased risk of transmitting HIV to their uninfected partners, because of both high viral load in early infection and lack of awareness of infection status. Identification and evaluation of persons in early HIV infection are critical to understanding the role of immunologic and therapeutic events and other interventions in early infection that could affect transmission rates and the course of HIV disease progression.

Coinfection of HIV-infected persons with other pathogens, including OIs and other STDs, may increase HIV replication, thereby increasing transmissibility of the virus and accelerating HIV disease progression. NIH-sponsored research has documented that it is possible to prevent initial and recurrent OIs. These studies have identified CD4 as a predictor of susceptibility to OIs, thereby identifying the populations to be targeted for primary prophylaxis.

Scientific Opportunities

Studies of the determinants of disease progression are of the highest priority in investigations of the natural history of HIV infection, because such studies will ultimately guide the development of preventive and therapeutic strategies. To this end, interdisciplinary studies of persons who appear to have reduced susceptibility to disease progression (nonprogressors, persons with low CD4 counts without clinical disease) may provide insights into correlates of protection from disease progression that may, in turn, focus preventive and therapeutic research strategies. Well-established, long-term cohort studies of seroincident participants provide a critical source of data and specimens for these studies. So far in the United States, such cohorts of seroincident cases have been composed primarily of groups of homosexual men, IDUs, and some newborns. These studies should be supplemented by cohorts of seroincident heterosexual men and women in developing countries, as well as in the United States, if possible. In addition, there is substantial value in cohort and case-control analysis of individuals with unusual outcomes who were not enrolled as seroincident cases.

Identification and validation of the best combination of predictors for specific outcomes (OIs or malignancies, survival) are critical in targeting interventions within populations. Such studies should evaluate the relative contribution of viral load, CD4 count, and clinical signs as predictors of specific outcomes and evaluate the utility of less expensive predictors in resource-poor environments. Because a large proportion of the global HIV pandemic is due to HIV subtypes not yet endemic in the United States, it is also important to perform cohort studies comparing the transmissibility and natural history of different HIV subtypes in international settings and to elucidate reasons for any differences that may be found.

Studies of the determinants of disease progression should include evaluation of the influence of viral subtypes and of variants within subtypes. Identification and validation of reliable predictors, such as viral burden, will be extremely useful in the effort to identify significant factors that affect the rate of disease progression and viral shedding. Potential cofactors to explore include host genetic factors, infectious agents, behaviors such as IDU and sexual practices, and nonpharmacotherapeutic interventions, such as nutritional supplementation, exercise, and health-enhancing behaviors. It is essential that research efforts to elucidate mechanisms of disease progression shift from studies evaluating laboratory assays of limited clinical applicability to studies evaluating assays properly tested in well-designed epidemiologic investigations and proven to be reproducible and stable.

An interdisciplinary program of research involving epidemiologic, clinical, behavioral, social, and laboratory science is needed to enhance identification and investigation of individuals with primary HIV infection for public health as well as individual health reasons. Behavioral and therapeutic interventions implemented early in infection may interrupt transmission.

Identification of newly infected persons is important to evaluate the effect of early therapeutic intervention on infectiousness and on long-term outcome. In addition, exploration of immunologic mechanisms for control of viral replication in early HIV infection may provide insights for vaccine development and therapeutic interventions. These studies can best be carried out in cohorts of high-risk, uninfected persons to avoid bias from referral-based case identification.

A systematic approach to the identification of persons at increased risk for OIs and effective intervention strategies should be implemented. Specifically, markers other than CD4 count for increased susceptibility to specific OIs should be a focus of investigation. In addition, reasons for the success and failure of chemoprophylaxis and lifelong suppressive therapy, including microbial resistance, are beginning to be evaluated in cohort studies and clinical trials. Additional exploration, however, is required. For those opportunistic pathogens that cannot be prevented effectively or treated with current antibiotic regimens, further research is needed immediately. This research should evaluate how health and well-being are affected by preventing exposure to suspected sources of infection, such as cryptosporidiosis and cytomegalovirus. This research also should study how different life situations, such as homelessness, affect exposure to and disease from OIs. Very rare outcomes, such as certain OIs or neoplasms, may be difficult to study within the framework of cohort studies, necessitating the use of case-control studies.

Recommendations

II.D.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.

II.D.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.

II.D.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.

II.D.4. Identify biological and sociobehavioral risk factors for OIs and evaluate the potential of targeting these risk factors in preventive interventions.

II.D.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.

E. Methodology Subpanel Report

HIV prevention policy and practice can be promulgated by a variety of different types of research studies including purely observational studies (e.g., case-control, cohort, network, and aggregate data studies), quasi-experimental studies, and purely experimental studies (e.g., RCTs). Among these different approaches to prevention research, a carefully conducted RCT with HIV infection as the primary endpoint can be regarded as providing the most reliable evidence of the efficacy of an intervention to prevent HIV transmission. Under certain circumstances, however, adequate evaluation of interventions may be obtained by less costly observational or quasi-experimental studies. Thus, the different approaches to prevention research should be viewed as complementary rather than competitive.

HIV intervention research should be expanded. While many promising preventive interventions could potentially contribute to the control of the epidemic (Table 1), few strategies have been rigorously evaluated. Reliable information about the efficacy of different intervention strategies to prevent transmission of HIV is urgently needed.

Methodologic guidelines for HIV prevention trials can be viewed as analogous to the trial-phasing system used in clinical trials of new pharmaceutical products (Table 2). These guidelines describe an orderly sequence of 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. The guidelines also describe research methodology appropriate for each phase of prevention research.

Not all intervention strategies should be evaluated with RCT methods. RCTs are most appropriate in HIV prevention research when the intervention involves new technology or novel application of existing technology; when the intervention is feasible and randomization is ethical; when small effects of the intervention are anticipated but the population-level impact on transmission may be large; and when important confounding factors in observational studies (e.g., exposure to HIV through sexual behavior) cannot be measured with reasonable accuracy and precision. RCTs may not be appropriate for evaluation of interventions that are inexpensive, uncontroversial, and have no new policy implications. RCTs also may not be appropriate when the interventions involve biological mechanisms that are obvious, when large effects are expected, or when important confounding factors in a quasi-experimental design can be reasonably measured and appropriately accommodated in the analyses of study data.

Because of the potential for an intervention to have both direct and indirect effects on transmission of HIV, assessment of intervention effects at the community level plays an important role in HIV prevention research, even for those interventions that are delivered at the individual level (e.g., prophylactic vaccines). In addition, interventions that are delivered to entire communities rather than to individuals within communities hold considerable promise for control of the epidemic and for being least costly. Thus, study designs in which entire communities are randomized to control or intervention conditions are likely to play a major role in HIV prevention research. Community randomized study designs pose considerable methodologic challenges. Much methodologic research recently has been conducted on this

topic but primarily in the context of prevention of chronic diseases. Some of these methods might be adapted for application to community randomized trials in HIV prevention research. New methods also will likely need to be developed and evaluated. Methodologic issues that should be addressed include community subsampling designs to obtain information regarding mechanisms of action of the intervention, methods for monitoring subpopulations that are important with respect to transmission of HIV within communities, and methods for monitoring efficiency and robustness of statistical analytic strategies.

An important emerging area of epidemiologic research has the goal of understanding the structure of social networks and the transmission of HIV within these networks. However, a comprehensive and theoretically sound methodologic basis for this work has not been articulated. This methodology should be theory-based but practically oriented and, ideally, should be developed by a multidisciplinary team including theoretical and applied statisticians, modelers, epidemiologists, sociologists, and anthropologists actively engaged in field research. This methodologic research should include formulation of population-based models for social networks that acknowledge the dynamic nature of these networks, the development of efficient study designs and practical sampling methods, and the development and evaluation of associated statistical analytic methods that take appropriate account of study design (e.g., the lack of statistical independence of observations) and accommodate missing and inaccurate data.

Establishing a system for reporting and evaluating current and completed HIV prevention research studies could greatly facilitate the focus of new research initiatives in the areas of highest priority. Research efficiency would increase by avoiding redundancy of projects. Such a system should include "structured abstracts" and study result reports that include descriptions of the specific study design and analytic methodology employed. As part of this endeavor, a comprehensive database of ongoing and completed HIV prevention studies should be established and made widely accessible.

Recommendations

II.E.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.

II.E.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.

II.E.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.

II.E.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.

III. Review of Natural History, Epidemiology, and Biomedical Prevention (NHEBP) Research at the NIH by Scientific Priorities

Overall, the NHEBP Panel endorses the research priorities developed for FY 1996 by the NIH OAR Natural History and Epidemiology Coordinating Committee, both in terms of content and relative rank order. The Panel attempted to assess the level of FY 1994 NIH funding corresponding to these 1996 priorities. The total research funding coded by ICDs as natural history, epidemiology, or prevention was $180 million. The coding system was not very helpful in defining the research being funded by the NIH in relation to natural history, epidemiology, or prevention and was almost useless as a meaningful classification of research within those priorities. However, the Panel reviewed major programs and the distribution of R01 support within its purview at each ICD and concluded that approximately $121.6 million, or two-thirds, was actually supporting research on NHEBP. Certain large categories attributed to NHEBP (i.e., 10 percent of the ACTG and the Community Program for Clinical Research on AIDS [CPCRA], certain large programs in NHLBI, etc.) were not considered related to current NHEBP priorities. Conversely, although the HIV Vaccine Efficacy Trials Network (HIVNET), the Fogarty International Center (FIC), NIDA Cooperative Agreements, and certain other projects were not coded as NHEBP, a substantial proportion of these programs should be so coded. Thus, perhaps $130 million, or about 10 percent of the total NIH AIDS research budget, is currently allocated to NHEBP.

Of the $121.6 million coded as NHEBP and considered by the Panel to represent NHEBP research, the approximate distribution of funding is as follows:

Natural History and Progression	$73 million
HIV Transmission	$38 million
Biomedical Intervention Research	$10.6 million

Within the category of biomedical intervention research, about $3 million was allocated to biomedical intervention trials. Even if much of the HIVNET and FIC budgets were reallocated to this category, it seems clear that much less than 1 percent of the total FY 1994 NIH AIDS budget was allocated to one of the highest priority research areas.

Definition of AIDS-Related Research

Certain ICDs did not have clear or useful definitions of AIDS-related NHEBP research. Certain Institutes (e.g., NIAID and NICHD) have carefully and proactively defined what is AIDS-related research, and other Institutes could emulate such a definition process.

Health Services Research

This important area was not assigned to any of the Area Review Panels. The Agency for Health Care Policy and Research (AHCPR) has major responsibility for such research, as do other Federal Agencies. Health services research is an important area to include in discussions of biomedical (and other types) of HIV preventions.

Declining Intramural and Extramural Strengths in Epidemiology

The departure, without evident plans for replacement, of several senior NIH intramural and extramural epidemiologists involved in AIDS research corresponds to growing importance of AIDS-related prevention research. This growing constraint on the NIH ability to plan, manage, or participate in prevention science programs must be addressed by the OAR.

IV. Review of Natural History, Epidemiology, and Biomedical Prevention Research at the NIH by Institute and Center

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

Epidemiologic research within NIAID (with a total of $66,573,850 classified as NHEBP) is conducted primarily by the Division of Acquired Immunodeficiency Syndrome (DAIDS) and the Division of Microbiology and Infectious Diseases (DMID). Major programs with funds coded as NHEBP include the Adult and Pediatric ACTGs and the Terry Beirn Community Program for Clinical Research on AIDS (CPCRA), which accounted for $15,500,000; the three natural history cohorts—the Women's Interagency HIV Study (WIHS), the Multicenter AIDS Cohort Study (MACS), and the Women and Infants Transmission Study (WITS)—$15,875,000; unsolicited investigator-initiated research, $13,155,000; and the Sexually Transmitted Disease Clinical Research Centers (STD-CRC), $4,367,000. NIAID also reported that a small portion ($1,670,000) of the research sponsored by HIVNET was classified as NHEBP research. However, a significantly larger portion of the $12 million allocated for HIVNET's 17 university sites, master contractor, and coordinating center actually supported critical NHEBP research. Finally, approximately $437,000 was committed by NIAID to intramural NHEBP research.

Seropositive Cohort Studies

The three natural history cohorts funded by NIAID (MACS, WITS, and WIHS) vary in duration, productivity, and potential. The MACS has made significant contributions to understanding the natural history of HIV infection in homosexual men. The current focus of this study is on unique outcomes in infected participants, including rapid progressors, men who demonstrate long-term immunologic stability, men who remain clinically stable at low CD4+ lymphocytes counts, and men who remain seronegative despite continued high-risk behavior. Two laboratories were funded in 1995 to conduct in-depth studies of virologic and immunologic determinants of unique outcomes in MACS participants.

The WITS, a multicenter investigation of determinants of vertical transmission, has to date failed to yield scientific information commensurate with the NIH investment. Although the investigators have enrolled and retained a large number of mother-infant dyads, only within FY 1995 have funds been made available for appropriate immunologic and virologic studies. The cohort of HIV-infected infants and uninfected infants exposed to AZT *in utero* is a unique resource that should be exploited to define the natural history of HIV infection and AZT exposure in children.

The WIHS, established in parallel to the CDC-funded HIV Epidemiologic Research Study in Women (HERS) to evaluate the national history of HIV infection, has enrolled 2,000 infected and 500 uninfected women, 75 percent of whom are women of color. The WIHS should be reevaluated. Such an evaluation should include a focused assessment of the need for 10 sites (6 WIHS, 4 HERS) studying HIV in women and the inclusion of seronegative women in the WIHS. The investigators should focus on hypothesis-driven research issues unique to women, such as shedding of HIV in vaginal and cervical secretions, mucosal immunity, and gynecologic manifestations of HIV disease (specifically those manifestations common enough to be measured in this cohort and not well-addressed in other investigations). The investigators also should explore the mechanisms underlying gender differences in specific outcomes. The research objectives should be feasible within the constraints of sample sizes available. The future focus for both the WIHS and the WITS should be on exploiting the unique features of each cohort and ensuring that the investigations capitalize on the expertise of laboratory, social, and behavioral scientists in addition to the expected contributions of clinicians and epidemiologists.

HIVNET Seronegative Cohort Studies

The HIVNET, established at eight domestic and nine international sites, has successfully recruited large cohorts of high-risk uninfected individuals. Although originally conceived as a network of cohorts for Phase III vaccine efficacy trials, the HIVNET can and is being used more broadly for a number of studies identified as priorities of this Panel, including investigation of exposed-uninfected persons, persons with early HIV infection, and controls for breakthrough infections in Phase I/II vaccine trials as well as evaluation of other nonvaccine prevention interventions (e.g., use of topical microbicides and perinatal prophylaxis interventions). In addition, HIVNET is collecting baseline data useful in determining the feasibility of conducting future vaccine efficacy trials and building support and educating local at-risk communities for prevention trials. Presently, HIVNET has RCTs in the field that are investigating immunoprophylaxis at delivery and microbicide use in commercial sex workers. In addition, 21 trial concepts have been developed by four ongoing scientific working groups: vaccine, microbicide/STD, perinatal, and behavioral. Six of these concept plans have been selected for full protocol development and will be implemented as multicenter prevention/intervention trials in FY 1996.

Scientific Review

Cohort studies should be reviewed periodically by a multidisciplinary panel to ensure that the original scientific rationale remains relevant and that important new opportunities for

significant research are not missed. Longitudinal cohort studies represent a fundamental component of prevention science. Such cohorts are often difficult to assemble but, once established, should represent a resource for a broad range of scientific questions to investigators from various disciplines, often supported by different Institutes. Therefore, such reviews should focus on the evolving potential scientific contributions of the cohort to all relevant ICDs, not solely on the relation of the project to the programmatic agenda of a specific Institute. Emphasis should be placed on coordination of epidemiologists, behavioral and social scientists, clinicians, virologists, and immunologists. The frequency of such reviews should be varied according to the productivity of the study and performed in a manner that does not interfere with the conduct of the project.

Clinical Trials

The adult ACTG has focused primarily on antiretroviral regimens and use of chemotherapy to prevent OIs in HIV-infected persons. Protocols have created cohorts followed for only 2 to 3 years, a period not sufficient for natural history studies. To date, the protocols have not evaluated the impact of antiretroviral therapy on mucosal shedding of HIV, a potential surrogate for HIV transmission. The pediatric ACTG has established a data base that could be utilized to investigate the natural history of HIV infection in children. In addition, the ACTG 076 trial documented the impact of antiretroviral therapy on vertical transmission, and trials of various chemotherapeutic and immune-based therapies are planned to evaluate other means of blocking vertical transmission. The CPCRA conducted a large investigation of the natural history of HIV infection as an initial study, but the generalizability of the data is limited, in that participation was drawn from persons already in the health care system. With some exceptions, such as the ACTG 076 trial, the Panel did not view the NHEBP-related efforts of the ACTG and CPCRA as contributing in a meaningful way to NHEBP research. This is a significant finding, since ACTG and CPCRA efforts represent a sizable proportion of the total NIAID NHEBP budget.

Intramural Studies

The intramural program of NIAID has focused on defining unique epidemiologic, clinical, virologic, and immunologic features of HIV-1 and HIV-2 infection in Africa, Asia, the Caribbean, South America, and the United States. These studies have investigated HIV infection in commercial sex workers, vertical transmission, heterosexual transmission, and HTLV-1/HIV co-infection. The investment by NIAID is relatively small, and these investigations have been extremely productive. The interaction of these studies with similar intramural studies funded by NCI and with NIAID extramural cohort studies should be augmented.

Investigator-Initiated Research

Unsolicited, investigator-initiated research designed to increase knowledge of pathogens that potentially augment HIV transmission or complicate established HIV infection is, in general, of high quality.

Recommendations

IV.A.1. Redirect NHEBP funding within the clinical trials networks to evaluate the effects of antiretroviral therapy on mucosal shedding of HIV.

IV.A.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.

IV.A.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.

IV.A.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.

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

NHLBI reported that approximately $35,491,048 of its extramural portfolio was devoted to NHEBP research. Examples of relevant activities that deserve continued or even increased support by NHLBI include efforts to facilitate the wider use of repository specimens from the transfusion-associated virus studies, implement multi-Institute trials of HIV immune globulin for the prevention of perinatal transmission, and develop sensitive and inexpensive alternative tests for detecting HIV infection in blood during the earliest stages of the disease. Investigations of pulmonary, cardiac, and hematologic complications of HIV infection are likely to provide useful insights into the pathogenesis as well as the epidemiology and natural history of the disease.

A substantial proportion of NHLBI funds allocated to NHEBP research, however, appears to be tangential to the major current research priorities in this area of emphasis. For example, although protection of the domestic blood supply from HIV and other transmissible agents has been of paramount importance to NHLBI, the threat of HIV-1 in this supply has diminished to the point where funds supporting this work can be redirected, especially toward inexpensive techniques for screening blood in the developing world. Another example of research that may be important in its own right but not immediately relevant to HIV epidemiology and prevention is development of blood substitutes. NHLBI has decreased the amount of AIDS funds supporting research on blood substitutes and should be encouraged to continue to do so, particularly research that has become less relevant as the U.S. AIDS epidemic has matured.

Recommendations

IV.B.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.

IV.B.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.

IV.B.3. Accelerate plans to publicize the availability of potentially valuable biologic materials in repositories from studies of transfusion-associated HIV infection.

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

The NHEBP portfolio of NICHD totals $17,048,263 and is the third largest at the NIH. The greatest proportion of these monies ($9,181,694 or 54 percent) is aimed at defining the effects of HIV infection on infant, child, and adolescent development and survival. However, in keeping with its unique mission to ensure the healthy development of individuals from conception to adulthood, NICHD has directed more of its NHEBP efforts to prevention than any other ICD. In addition to behavior-based prevention research, NICHD sponsors biomedical-based prevention research, which includes studies to evaluate the use of nonlatex condoms ($448,000), antimicrobial spermicides ($1,464,000), and combination female-controlled methods ($522,000). NICHD also conducts postmarketing surveillance to assess the utility of existing barrier contraceptives to prevent HIV transmission/acquisition ($636,000). The R01 portfolio includes investigator-initiated studies of biomedical prevention methods involving breast-feeding practices, vitamin A supplementation, and vaginal cleansing before childbirth. All of NICHD's NHEBP research targets special populations, including adolescents and pregnant women. The Institute also has one of the more diverse portfolios in terms of funding mechanisms, with approximately equal amounts ($4 to $5 million) allocated to contracts, cooperative agreements, and unsolicited investigator-initiated research grants.

The research portfolio at NICHD covers three general areas pertinent to the priorities of this Panel: sexual and other risk-taking behaviors; reproductive health; and maternal, child, and adolescent health. NICHD has, more than most other ICDs, maintained a good overall coordination of its HIV research efforts both within the NIH and other U.S. Public Health Service agencies. Moreover, research activities categorized as AIDS-related are accurately labeled.

NICHD supports innovative behavioral research that uses national surveys of sexual behavior and employs innovative survey methodology. This research is crucial to understanding sexual behavior in its social context (e.g., sexual networks) and to developing effective interventions. NICHD-supported research on the molecular aspects of reproductive function and physiology is

important for defining mechanisms for sexual transmission of HIV. The Institute's support of the simian immunodeficiency virus (SIV) model is helpful for examining aspects of infectiousness and host susceptibility. NICHD's emphasis on contraceptive research has provided essential knowledge on the safety and efficacy of barrier methods. Finally, the natural history of pediatric infections is being defined through its pediatric and perinatal clinical trials network.

The Panel observed some gaps in the NICHD-funded programs that were reviewed. To address these gaps, NICHD should shift perinatal HIV resources from domestic to international sites to better define ways to prevent perinatal transmission, including contraceptive use by HIV-infected women, and should increase the use of RCTs to assess how STD/HIV transmission is affected by the choice of contraceptive methods, such as barrier methods, hormonal contraception, and the use of intrauterine devices. It will be necessary to address the ethical complexities of contraceptive choice that have to date limited these studies. NICHD also should more actively pursue molecular aspects of the sexual transmission of HIV (e.g., study HIV shedding in contraceptive users and the role of mucosal factors in HIV transmission and acquisition) and more fully develop an integrated adolescent research agenda with consideration of behavioral, biological, and sociocultural factors important in natural history and prevention. Targeted research on new contraceptives, especially those with the greatest efficacy against sexual transmission of HIV, should be encouraged.

Recommendations

IV.C.1. Shift perinatal HIV resources from domestic transmission studies to international prevention studies.

IV.C.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.

D. National Institute on Drug Abuse (NIDA)

NIDA's research portfolio in this area is $16,036,704, of which about $11 million is devoted to the scientific priorities outlined by this Panel. NIDA has awarded approximately $6 million for prevention trials, most of which are not designated as natural history or epidemiology. Much of the NIDA research reviewed is funded using the R01 mechanism; a smaller proportion is funded using cooperative agreements. Program-driven mechanisms will be needed to ensure that NIDA can implement the research priorities as outlined in this report.

Since a large proportion of incident HIV infections in the United States have occurred among IDUs, crack cocaine smokers, their sexual partners, and their infants, NIDA bears a responsibility for research in IDU-related AIDS epidemiology, natural history, and prevention. NIDA's funding of cross-sectional studies and cohort studies has afforded a good picture of which individual behaviors are risk factors for HIV transmission and has contributed to the

knowledge of HIV disease progression. However, at this time, it is appropriate to reorient the research to build on what has already been learned and to develop needed knowledge in highly promising areas that have received less attention to date.

NIDA should take a leading role in studying the most effective ways to facilitate access to sterile syringes and needles for the prevention of HIV. Specifically, Phase II research should be conducted to determine component elements of the most efficacious syringe exchange programs or area-wide mixes of programs (which may include pharmacy distribution), followed by Phase III trials of different models of sterile syringe and needle distribution and removal. In addition, NIDA should study the social and ecological epidemiology of HIV among IDUs and crack cocaine smokers to determine the reasons for differences in HIV prevalence and incidence by geographical area, race/ethnicity, and other factors. This effort should include studies of multicity data on HIV prevalence and incidence, assess the extent of IDU and crack cocaine smoking, and determine how and why the social networks of IDUs and crack smokers vary by geographic area and how these networks affect HIV transmission. Network techniques could be used to attempt to resolve some of the existing puzzles, such as why IDUs who also are African American, Puerto Rican, or women who have sex with women are more likely to become infected with HIV than are other IDUs.

NIDA should place a priority on sponsoring studies to (1) determine the role of drug paraphernalia laws on the spread of HIV infection; (2) assess the interaction of drug-related behaviors on viral type, viral load, and/or shedding and their effects on transmission and disease progression; (3) determine the natural history and survival of HIV in syringes and other drug-injection paraphernalia; (4) develop effective chemotherapy and behavioral treatments for drug dependency, including cocaine dependency (to the extent that the direct relationship of such treatment to HIV infection is the major focus); and (5) assess methods to decontaminate potentially infected syringes.

Recommendations

IV.D.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 effect initiation of drug injection.

IV.D.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.

E. National Cancer Institute (NCI)

The NHEBP research portfolio funded by NCI totals $14,728,01 and is conducted within the Epidemiology and Biostatistics Program of the Division of Cancer Etiology. This comprises approximately 8 percent of the total NHEBP funding. The extramural portfolio ($8,396,245) is based within the Extramural Programs Branch; the intramural portfolio ($6,331,766) is based within the Viral Epidemiology Branch, which was created in 1993 following the reorganization of the Environmental Epidemiology Branch and the Biostatistics Branch.

The objectives of NCI's extramural program in HIV/AIDS epidemiology are to determine the incidence, prevalence, and time trends for the occurrence of HIV-related malignancies; to define the risk factors for cancer development in HIV-infected individuals; to clarify etiologic mechanisms; and to elucidate the role of retroviral infection and viral coinfection in neoplastic processes. Initiatives have included a cooperative agreement targeted toward epidemiologic studies of HIV-associated malignancies and program announcements in support of epidemiologic studies of cancer and human retroviruses. Discussions are under way to support a component on HIV-associated malignancies (primarily anogenital cancers) that would be nested within the WIHS. Future directions of the Extramural Programs Branch include expanding surveillance of various subpopulations of HIV-infected individuals to determine the incidence and mortality of HIV-related cancers, such as anogenital dysplasias, Kaposi's sarcoma, and non-Hodgkin's lymphoma.

NCI's intramural research program in HIV/AIDS epidemiology and biostatistics is unique to the NIH. The Viral Epidemiology Branch could serve as a prototype for any future intramural HIV/AIDS epidemiology facility. The goal of the Branch is to elucidate and prevent HIV infection, malignancies, and other consequences of AIDS. Branch contracts fund studies of HIV and related viruses, a repository of biological specimens from persons at high risk of cancer, studies of retrovirus epidemiology, and studies of HIV among hemophiliacs and their sexual partners. Notably, the contracts also support international epidemiologic surveys of human retroviruses, studies of the epidemiology of HTLV-I in leukemia/lymphoma in Trinidad and the Caribbean region, a study of HTLV-I in Jamaica, and studies on the epidemiology of potentially oncogenic and immunosuppressive viruses in West Africa. Because this Panel did not have the opportunity to review the scope of this work at the NCI's Frederick Cancer Research and Development Center (FCRDC), these activities should be reviewed in the future.

The major future emphasis of the intramural research program should be on continued studies of the epidemiology of human retroviruses (especially HIV-1) that make maximal use of already established research infrastructures, such as the Multistate AIDS-Cancer Match Registry, the Multicenter Hemophilia Cohort, and research collaborations developed in the West Indies and in Africa and the carefully characterized prospectively collected biologic materials associated with these projects. Significant emphasis should be placed on molecular epidemiology.

Recommendations

IV.E.1. Focus on epidemiologic research of AIDS-related and retroviral-associated cancers.

IV.E.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.

IV.E.3. Actively pursue expanded linkages to cohorts funded by other ICDs to maximize opportunities to study HIV-associated malignancies.

F. National Institute of Mental Health (NIMH)

The NIMH Office on AIDS supports an active program of NHEBP research totaling $11,975,424. These funds are being appropriately spent in support of investigator-initiated R01s as well as CFARs, and multidisciplinary training programs. Much of the relevant portfolio at NIMH lies at the intersection of epidemiology and behavioral science. Consequently, some individual projects and programs have been characterized by NIMH as belonging in both scientific domains.

Transmission and Biomedical Prevention

The central focus of the NIMH research portfolio allocated to NHEBP is social and behavioral epidemiology of risk-relevant behavior in diverse at-risk populations, e.g., gay men, adolescent runaways, women, and homeless chronically mentally ill persons. A strength of this program has been studies at the individual and community levels that are identifying risk behaviors associated with HIV transmission. This research has helped explain differences in HIV prevalence by documenting differences in social norms that affect attitudes about prevention in various networks of persons at risk. Another strength of this program is the set of national surveys assessing beliefs about effectiveness of STD prevention programs.

The NIMH Office on AIDS has given the highest priority to the development of primary prevention strategies based on the social and behavioral epidemiologic research. The findings from clinical trials on behavior-change strategies are relevant to the primary prevention/ intervention strategies addressed by this Panel. One of the funded trials is a multisite RCT directed at primary prevention of HIV transmission in women who are seen in primary care settings and in men and women who receive care at STD clinics. This trial is evaluating the efficacy of behavioral interventions on STD rates as well as self-reported changes in behavior (see also the Behavioral, Social Science, and Prevention Research Area Review Panel Report). More recent studies supported by NIMH are investigating and advancing the science of maintaining behavior change. The results of these studies are directly applicable to biomedical prevention approaches.

International research relevant to behavioral epidemiology and prevention of HIV transmission has been supported by NIMH. Included in this portfolio are studies to assess the impact of HIV counseling and testing on use of condom and spermicides and to determine the subsequent effects on HIV seroconversion and STD rates among African women and men. Newer studies have extended this research to countries with more recent epidemics, such as India.

Natural History and Disease Progression

The NIMH supports longitudinal studies of HIV-infected persons to examine illness complications related to psychological, neuropsychological, and cognitive functioning, as well as pain and complications related to lifestyle factors. NIMH has funded research investigating relationships between these complications and clinical outcomes. Other studies examine social and behavioral factors that might mediate the adverse consequences of HIV infection, including social support, family caregiving, and access and adherence to care. Some of these studies have examined the association of social and behavioral factors such as bereavement or HIV-related stress on CD4 levels and changes in immunological variables in HIV-infected persons (see also the Behavioral, Social Science, and Prevention Research Area Review Panel Report).

The NIMH is well equipped to extend its research on disease progression, much of which is relevant to the behavioral arena. The NIMH is conducting randomized trials to test the impact of interventions focused on increasing adherence to clinical trial and prophylaxis regimens and on treating complications of HIV infection such as depression. Recently, additional RCTs have been conducted to test the effect of modifying lifestyle factors, such as coping ability and exercise, on quality of life and adherence to care. NIMH has important contributions to make to studies designed to characterize persons with unusual outcomes and to investigate the role of cofactors in disease progression. Among the priorities and recommendations is the call for strategies for preventing exposure to OIs and identifying markers for increased risk of developing OIs and other HIV-related outcomes. This research would likely create opportunities for developing interventions to effect behavior changes that could slow disease progression. Collaboration with other ICDs including NIAID and NICHD will be important to capitalize on NIMH contributions to research on natural history and disease progression.

The NIMH has a strong research program focusing on central nervous system (CNS) effects of HIV infection and AIDS. These programs investigate not only the direct effects of HIV on CNS function and subsequent neurological and behavioral manifestations but also focus to some degree on OIs that can involve the CNS. These programs have incorporated a broad range of methods, from neurobehavioral to electrophysiological. In addition, there has been a focus on prevention of CNS effects of HIV. These efforts interface with those in the pathogenesis arena. Accomplishments have been substantial. Further collaboration between NIMH and the National Institute of Neurological Disorders and Stroke (NINDS) to incorporate research into these factors broadly across the nervous system would be helpful.

Collaboration with Other ICDs

In pursuit of its mission, the NIMH Office on AIDS collaborates with most of the other relevant ICDs. For instance, it is cofunding projects with NIDA, NIAID, NICHD, NINDS, and NHLBI that are directly relevant to social and behavioral epidemiology, prevention, pathogenesis, and the natural history of HIV infection.

Recommendations

IV.F.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.

IV.F.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.

G. Fogarty International Center (FIC)

The FIC AIDS International Training and Research Program (AITRP) provides training of foreign scientists in conducting epidemiologic and prevention research and clinical trials and supports collaborative research between U.S. and foreign scientists. Of the 15 AITRP awards, 11 are international training grants in AIDS epidemiology and 4 are postdoctoral AIDS research training grants. During its first 6 years of the program, the U.S. university-based AITRP program provided training in the United States to 1,000 health professionals from 70 countries/territories, primarily from Africa, Asia, and Latin America. The FIC also supports in-country training and has so far supported 400 training courses attended by 25,000 trainees. By next year, the AITRP will have extended to 80 countries and territories, a remarkable achievement during the first 6 years of effort. The recent expansion of the AITRP program to Asia, Eastern Europe, and the former Soviet Union is very appropriate. Two other important FIC initiatives are the Minority Investigator Research Training (MIRT) program, which provides training opportunities for U.S. minority health professionals, and the Fogarty International AIDS Research Collaboration Awards (FIRCA) program, which was initiated in 1994.

The FIC has been instrumental in supporting training in epidemiology, which is an easily transferable and necessary AIDS research discipline in developing countries (compared with molecular virology, for example, which is less transferable). The linkages with the vaccine preparedness program and other agencies for prevention-oriented research represent a highly appropriate priority for developing countries. Many current prevention trials under way in developing countries depend on the infrastructure and expertise developed by the FIC programs. This panel believes many of these clinical trials could not have been developed without the

AITRP. As the FIC training program has matured, the selection of trainees likely to remain in research has improved, and FIC trainees have proven invaluable to NIH-funded international research. Many of these trainees have had outstanding productivity after completing training. However, not unexpectedly, a main constraint for reentry into academic and public health careers in the home country has been availability of continuing research funding and salary support. In view of the outstanding success of the FIC AIDS training program in establishing research linkages between U.S. universities and foreign scientists in prevention research, the program should be continued and increased support considered for reentry research funding of high-caliber trainees, perhaps analogous to the Research Career Development Award mechanism but linked to a U.S. institution.

Recommendation

IV.G.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.

H. Other Institutes and Centers

The **National Center for Research Resources (NCRR)** codes somewhat less than 10 percent of its AIDS budget ($4,651,585) as NHEBP research. Most of these funds are allocated for the support of General Clinical Research Centers (GCRCs) and Regional Primate Research Centers (RPRCs). The GCRCs appear to support small, focused epidemiologic studies in cohorts or therapeutic clinical trials. While these efforts are appropriate, several of the largest grants seem to provide funds to existing cohort studies (which have their own support) rather than supporting focused studies within these cohorts. The concept behind the GCRCs Research Centers in Minority Institutions Program is sound, but it is difficult to assess the quality of the research being performed. RPRC-sponsored animal model studies of maternal-fetal transmission also are appropriate, but it is not clear whether these studies are coordinated with studies conducted by NIAID or NICHD. Moreover, coordination of studies among RPRCs appears to be lacking, and the studies appear to be operating without an overall research agenda.

The **National Institute of Dental Research (NIDR)** coded $3,364,236 for NHEBP research that was directed toward collaborative efforts with major cohort studies, with the goal of elucidating the oral manifestations of HIV infection in selected populations (homosexual men, IDUs, hemophiliacs, children, women, and minorities.) The NIDR research in this area is conducted primarily within the intramural Epidemiology and Oral Disease Prevention Program, which has linkages with the WIHS, the Walter Reed Army Institute of Research, and NICHD. The Walter Reed cohort has enrolled over 800 military personnel, of whom 50 percent are from minority populations. The WIHS collaboration will allow comparisons of oral lesions with other mucosal lesions, especially the hierarchy of candidal infections of the mouth, esophagus, and genital tract. These collaborations are good examples of how an Institute with a relatively

small AIDS budget can maximize the opportunities for research that fulfills the Institute mission.

The **National Institute of Neurological Disorders and Stroke (NINDS)** coded $2,517,019 for natural history and epidemiology AIDS projects centered around determinations of the neurological sequelae of HIV infection, both early in infection and in the later stages of AIDS. Funding includes R01s, a program project grant, and other funding mechanisms. Projects investigate a wide variety of neurological problems, including AIDS Dementia Complex, grey matter neuropathy, and the effect of HIV on the development of the nervous system. These projects have an exclusive focus on the effects of HIV itself on the nervous system.

Because HIV has dramatic effects on the nervous system (effects which can be difficult to treat and which can pose severe problems for persons with late-stage AIDS), NINDS-funded investigations of these effects are important. NINDS could increase the focus on the neurological problems associated with HIV disease by sponsoring studies to investigate the determinants of these disorders and exploring approaches to prevent them from occurring. Increased efforts of neuroscientists in this arena is warranted. Furthermore, a number of known OIs affect the nervous system, and an effort on the part of NINDS to approach these issues may prove quite fruitful.

The **National Institute of Nursing Research (NINR)** funds an intramural program ($346,139) composed of two projects. The first focuses on patients who develop myopathy during antiretroviral therapy and includes muscle biopsy and serum biochemical measures in addition to clinical performance. The second is a descriptive study of the epidemiology of fatigue in patients treated with interleukin-2. NINR research is not clearly within the NHEBP area of emphasis.

V. Special Issues

A. Funding Mechanisms

Extramural Research

Epidemiologic research on biomedical prevention, natural history, and disease progression requires interdisciplinary efforts and access to special populations. Central coordination is required for large-scale multidisciplinary efforts characteristic of epidemiological and prevention research, and such efforts require extensive collaboration between nongovernmental investigators and NIH program staff. The requirements for multicenter epidemiologic research may be better served, in some cases, by the use of directed types of funding mechanisms, particularly cooperative agreements, in conjunction with individual investigator-initiated R01 grants.

There are a variety of important questions and problems for which answers are unlikely to be sought through existing intellectual or financial research incentives. An example can be found

in the area of standardization and quality control. For several years after it became clear that quantification of CD4 cells would be a critical prognostic indicator in clinical and research settings, little effort was undertaken to standardize or improve technology until a program-directed effort was initiated. Similarly, perhaps unnecessarily long periods have elapsed in developing and field-testing such practical products as a microbicide that would kill HIV in injection paraphernalia, or low-cost low-technology methods for rapid HIV testing by blood transfusion services in resource-poor settings. These types of research may require program-directed funding.

Intramural Research

Intramurally funded research sometimes can be conducted with more flexibility than extramurally funded research, in that intramural epidemiologists may be in a position to respond more quickly than their extramural peers to topics of nascent interest and importance. Working closely with intramural laboratory scientists and extramurally funded investigators, intramural epidemiologists might instigate specific timely and topical research projects. Such research is not likely to emerge from peer-reviewed extramural investigators in as timely a fashion because of the 2-year lead time for initiation of new initiatives based on extramural funds.

The largest intramural program in HIV/AIDS epidemiology at the NIH is located in the NCI Viral Epidemiology Branch. A smaller intramural program in AIDS epidemiology, based paradoxically at The Johns Hopkins University, is a part of the NIAID Immunopathogenesis Laboratory. Other ICDs, including the NHLBI, NIDR, NICHD, NIDA, and NIMH, fund smaller intramural epidemiology research programs. Because the overall intramural NIH budget for NHEBP research, is small, the Panel did not extensively review programs other than the Viral Epidemiology Branch of NCI.

The recent loss of senior intramural and extramural epidemiologists from NCI and NIAID portends a decrease in intra-NIH research perspectives on behalf of epidemiology and prevention. Bridges built between intramural and nongovernmental epidemiologists could help maintain a NIH presence in epidemiology and biomedical prevention. The intramural programmatic support for the remaining epidemiologists must be maintained, particularly for innovative and fast-moving activities in the intramural arena. Possibly, the use of Visiting Scientists could be expanded in the area of epidemiology and prevention science. Although accountability for resource allocation and quality of intramural epidemiology must continue, particularly for NCI FCRDC laboratories, the Panel does not believe that the overall intramural epidemiology resources are excessive.

Recommendations

V.A.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.

V.A.2. Provide support and oversight for the Centers for AIDS Research programs that include biomedical, clinical, laboratory, and prevention science research.

V.A.3. Facilitate collaboration among NIH intramural and NIH extramural epidemiologists.

B. Peer Review

Several problems have been identified with regard to the current peer-review process and its ability to review proposals in the emerging interdisciplinary field of Prevention Science Research. For instance, current reviewers of HIV/AIDS epidemiology research emphasize methodology and often lack programmatic experience and expertise. Because of the needs in this area, the NIH should restructure an existing Initial Review Group (IRG), creating one or more multidisciplinary social/behavioral/biomedical HIV/AIDS Prevention Research study sections. In the interim, the prevention science NIH extramural program staff and the OAR should work to inform the existing study sections of its research priorities. For the review of large-scale coordinated research programs such as the WIHS, WITS, and HIVNET, mechanisms should to be implemented to improve outside peer review and to create avenues for ancillary studies by investigators with innovative, timely ideas who are not directly funded by the programs. Because epidemiologic research by nature is interdisciplinary, peer review is particularly problematic with regard to review and scoring by the IRGs. Therefore, creative alternatives to the usual process of assigning primary and secondary reviewers should be explored so that the review can benefit from the additional input by study section members from the required disciplines. Other possibilities include appointing more *ad hoc* reviewers, reviewing fewer proposals per IRG, or having more frequent but shorter (and perhaps electronic) IRG reviews.

Recommendations

V.B.1. Restructure an existing IRG to create a study section devoted to prevention science research.

V.B.2. Increase the interaction between prevention science NIH extramural program staff and existing IRGs so that program research priorities are understood more fully.

V.B.3. Consider alternatives to the usual designation of a primary and secondary reviewer when a project is highly multidisciplinary.

V.B.4. Improve mechanisms for peer review of research proposals funded by master contracts, such as the HIVNET.

C. Cross-Institute and Interagency Collaborations

The importance of multidisciplinary approaches in addressing research priorities cannot be overstated. ICD collaborations are one mechanism for promoting cross-disciplinary research. It appears, however, that there is a limited awareness of what research is being conducted among the institutes. The OAR could play a stronger role in encouraging and rewarding inter-ICD collaboration.

There also appears to be room for improvement in the levels of coordination and collaboration among the NIH and other HHS agencies in the development of research priorities. To the extent that NIH can influence HHS, this panel suggests that the HHS develop a review process to evaluate collaboration and coordination among agencies and to suggest mechanisms to enhance such collaborations. In particular, NHEBP research offers opportunities for increased communication and collaboration between the NIH and the CDC.

Recommendation

V.C.1. Commit to expanding and strengthening collaboration among ICDs within the NIH and among other Federal agencies.

D. Cross-Disciplinary Research: Overlap With Other Panels

The work of the NHEBP Area Review Panel naturally overlapped with the reviews of other panels, particularly the Behavioral, Social Science, and Prevention Research Panel (biomedical and behavioral prevention being appropriately intertwined); the Vaccine Panel (NIAID HIVNET studies); the Etiology and Pathogenesis Panel (specimen repositories, studies of molecular pathogenesis nested within cohort studies, neurologic manifestations of HIV); and the Clinical Trials Panel (observational studies nested within the clinical trial networks). The Panel found such cross-collaboration among Area Review Panels very helpful and endorses similar cross-collaboration across the OAR Coordinating Committees.

Recommendation

V.D.1. Extend the collaboration developed within the framework of the Area Review Panels to include the activities of the five OAR Coordinating Committees.

E. Links Among Research, Services, and Communities

There are potential bidirectional links of NIH NHEBP research to community groups. It is important that the NIH research agenda be open to community input. The presence of community advisory boards (CABs) has been an important development and can stimulate expanded support for prevention research within the community. A variety of community

groups have provided input into NIH research, and the NIH should continue to reach out to affected communities to educate them about prevention research and solicit their suggestions about NIH AIDS research efforts. Special efforts should be made to increase the inclusion of historically excluded groups in CABs.

Because of the traditional absence of advocacy for prevention in contrast to advocacy for treatment, the Panel recommends a variety of strategies to build constituencies to become involved in prevention advocacy for NIH AIDS research. Strategies could include encouragement of CABs for research projects with attention to dissemination of research results.

Recommendation

V.E.1. Extend the CAB models developed for clinical trial networks and cohort studies to include community involvement in the area of prevention science research.

F. Links Between the Public and Private Sectors

Historically, prevention science research has been uniquely unsuccessful in attracting the private sector. Nonetheless, AIDS research at NIH would benefit from increased public/private sector collaboration in at least two areas: (1) development of new technologies to prevent and/or treat HIV and (2) support of private organizations to allow more efficient coordination of multicenter research projects. First, a combination of public/private resources should be aimed at developing new biomedical technologies beyond the obvious treatments and vaccines, such as new technologies in the field of diagnostics (e.g., STD amplification techniques), treatment (e.g., immunoboosters), HIV prophylaxis (e.g., female-controlled barriers, microbicides, single drug injection instruments), and OI prevention. Factors inhibiting private investment in the above technologies include the political sensitivity of HIV/AIDS research and the sexual/IDU behaviors associated with HIV transmission, the potential for litigation when preventive products are used by healthy populations, and the many licensing requirements of the Food and Drug Administration (FDA) necessary to bring a new product to the marketplace. NIH should explore further creative use of Small Business Innovative Research Grants (SBIRs) and Collaborative Research and Development Agreements (CRADAs) with biotechnology companies to expedite the transfer of new products, such as inexpensive diagnostics for STD/HIV, from the laboratory to the marketplace. NIH also could collaborate more proactively with private donors (e.g., the American Foundation for AIDS Research) and sources of venture capital to stimulate biotechnical development and sociobehavioral research in the area of prevention as well as other areas of biomedical research.

Private organizations sometimes can facilitate distribution and review of research protocols, expedite the travel and conference calls necessary to promote scientific communication, and act as facilitators in promoting the large-scale, multicenter research necessary to provide answers to important HIV prevention questions. In addition, private companies can facilitate preparation of the necessary paperwork (e.g., investigational new drug applications) to obtain regulatory

approval by the FDA. NIAID has attempted to facilitate multicenter research in HIV prevention through the HIVNET mechanism. The HIVNET currently has two master contractors (domestic and international), a statistical contractor and a laboratory contractor, to assist in coordinating both HIV prevention and vaccine preparation studies in eight domestic and nine international sites. Mechanisms to ensure the scientific quality of proposals and protocols funded by this collaboration must be developed and maintained.

Recommendations

V.F.1. Proactively collaborate with private donors and other sources of venture capital to stimulate biotechnical development.

V.F.2. While exploring the AIDS research opportunities offered by private organizations, NIH should critically evaluate the efficiency and scientific productivity of master contract mechanisms.

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

HIV-related NHEBP research has generated extensive statistical data and sizeable repositories of biomedical specimens. Much of this material could be usefully analyzed beyond what is being done by the investigators (both NIH intramural and nongovernmental NIH-funded investigators) who have collected the data or specimens. Because collaborations with outside investigators often prove fruitful, encouragement of such research should be enhanced. In fact, considerable work would be necessary even to develop, much less maintain, a data base of what data and specimen repositories are extant.

Since large cohort and cross-sectional studies require substantial levels of funding, it is particularly important that as much be learned from these studies as possible. Mechanisms should be established to facilitate and maximize access to the data and specimens by qualified investigators not involved in the studies, with appropriate recognition of both the need to conserve specimens for future analyses and the proprietary interest/needs of those who conceptualized and implemented the research project. Criteria for access and utilization of data and specimens by qualified investigators have been developed for several of the major epidemiologic studies funded by the NIAID; these criteria should be reviewed for possible application to other studies.

Specimen repositories, in particular, are an extremely valuable resource, largely supplied by cohort studies. However, excellent science requires that the epidemiologists involved in designing and analyzing the cohort studies be involved in evaluating and refining studies proposed by other scientists seeking access to repository specimens. Streamlined mechanisms must be implemented to ensure that maximal use is made of precious specimens and that specimens are rapidly made available for promising studies. However, because collaborators often repeatedly request specimens from the same most informative cohort participants for whom only limited specimens are available (e.g., rapid progressors), it is critical that cohort

epidemiologists work with basic scientists to ensure the appropriate prioritization of requests, based on scientific need.

As data accrue from RCTs of epidemiologic prevention modalities, the NIH/OAR should establish collaboration teams to make the information and specimens more available for cross-comparisons and meta-analyses, perhaps in the manner of the Cochrane Collaborations already established for clinical trials of other diseases. The OAR Natural History and Epidemiology Coordinating Committee could investigate whether similar approaches would be useful for organizing ecological analyses of existing data and/or organizing meta-analyses.

Recommendation

V.G.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.

VI. CONCLUSIONS AND RECOMMENDATIONS

See Executive Summary.

Appendix A

Biographies of Panel Members

King Holmes, M.D., P.h.D., *Panel Chair*, is Director of the Center for AIDS and STDs, and Professor of Medicine, Epidemiology, and Microbiology, University of Washington, Seattle. Dr. Holmes received his M.D. from Cornell University Medical College in 1963 and his Ph.D. in Microbiology from the University of Hawaii in 1967. He completed an internship in Internal Medicine at Vanderbilt University and a residency in Medicine at the University of Washington, Seattle, and is board certified in Internal Medicine, with a Subspecialty in Infectious Diseases. Dr. Holmes served as Head of the Division of Infectious Diseases at the U.S. Public Health Service Hospital, Seattle, from 1970-1981, after which he joined the Centers for Disease Control and Prevention, Atlanta, as Assistant to the Director, Division of Sexually Transmitted Diseases. From 1989-1990, Dr. Holmes was based at the Epidemiology Support and Research Unit, Global Program on AIDS, World Health Organization, Geneva. He is a member of the Institute of Medicine.

Sandra L. Melnick, M.T.(A.S.C.P.), Dr.P.H., *Panel Executive Secretary*, is Coordinating Chair of Natural History and Epidemiology, Office of AIDS Research, Office of the Director, National Institutes of Health. Dr. Melnick received her M.P.H. in Epidemiology from the University of Alabama at Birmingham in 1982, and her Dr.P.H. in Epidemiology from the same institution in 1986, in addition to postdoctoral training at the University of Washington at Seattle. She was Assistant Professor of Infectious Disease Epidemiology at the University of Minnesota School of Public Health before joining the Epidemiology Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, in 1992, where she served as the Program Officer for the Women's Interagency HIV Study.

Moises Agosto is Director of Research and Treatment Advocacy, National Minority AIDS Council. Mr. Agosto's areas of expertise include research and treatment advocacy and issues specific to minority communities.

Susan Buchbinder, M.D., is Chief of the Research Branch, San Francisco AIDS Office, and Assistant Clinical Professor of Medicine and Epidemiology, University of California, San Francisco. Dr. Buchbinder received her M.D. from the University of California, San Francisco, in 1985 and completed a residency in Primary Care Internal Medicine at the same institution. She is board certified in Internal Medicine. Dr. Buchbinder's research focuses on issues related to gay men at risk for HIV infection and correlates of immunity as determined from transmission and natural history studies.

Victoria Cargill, M.D., is Associate Professor of Medicine, Case Western Reserve University, Cleveland. Dr. Cargill received her M.D. from Boston University School of Medicine in 1977 and a M.Sc. in Epidemiology from the University of Pennsylvania. She completed her residency in Internal Medicine at Peter Bent Brigham Hospital and is board certified in Internal Medicine. Her research is focused on AIDS in minorities, particularly minority adolescents, barriers to participation in AIDS clinical trials among women and African-Americans, and gender/race/ethnicity issues in HIV/AIDS.

Willard Cates, Jr., M.D., M.P.H., is Corporate Director of Medical Affairs, Family Health International, North Carolina. Dr. Cates obtained a masters degree in history from Kings' College, Cambridge University, Cambridge, England. He received a combined M.D.-M.P.H. degree from Yale University School of Medicine in 1971 and had clinical training in Internal Medicine at the University of Virginia Hospital. He is board certified in Preventive Medicine. Prior to joining Family Health International, Dr. Cates was at the Centers for Disease Control and Prevention, Atlanta, where he served as Director of the Division of Sexually Transmitted Diseases for 9 years. He also directed the CDC Division of Training, overseeing the CDC Epidemic Intelligence Service and the CDC Preventive Medicine Residency.

Margaret A. Chesney, Ph.D., is Professor of Medicine, School of Medicine, University of California, San Francisco. Dr. Chesney received a Ph.D. in Counseling-Clinical Psychology from Colorado State University and completed postdoctoral training in Psychiatry at Temple University School of Medicine. She is currently the Co-Director of the Center for AIDS Prevention Studies at the University of California, San Francisco, where she is engaged in research on the relationship between behavior and chronic illness, behavioral factors in clinical trials, the development and evaluation of behavioral treatments of health problems, coping with HIV, and women's health.

Samuel R. Friedman, Ph.D., is a Principal Investigator at the National Development and Research Institutes, Inc., New York City. He received his Ph.D. in Sociology from the University of Michigan at Ann Arbor. His current research focuses on social factors, social networks, and HIV risk among drug injectors; multisite national and international studies of risk behaviors and HIV among drug injectors; and studies of risk behaviors and parenterally and sexually transmitted infections among youth in high-risk neighborhoods. His areas of expertise include sociobehavioral science; social epidemiology; racial/ethnic variations in risk behaviors and in HIV/AIDS; risk factors for HIV among drug injectors; social and behavioral aspects of drug use; and research on methods of HIV prevention such as syringe exchange, drug users' organizations, and outreach.

Richard A. Kaslow, M.D., M.P.H., is Professor of Epidemiology, Medicine, and Microbiology, University of Alabama at Birmingham. Dr. Kaslow received his M.D. from Harvard Medical School in 1969 and his M.P.H. from the Harvard School of Public Health in 1976. He served as Epidemic Intelligence Service Officer with the Centers for Disease Control and Prevention, Atlanta. Dr. Kaslow completed his residency in Medicine at Mount Sinai Hospital in New York and the University of California, San Francisco; this was followed by a fellowship in Infectious Diseases at Children's Hospital Medical Center-Beth Israel Hospital. Dr. Kaslow is board certified in Internal Medicine, with a Subspecialty in Infectious Disease, and in Preventive Medicine. He was Chief of the Epidemiology and Biometry Branch, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, prior to joining the University of Alabama at Birmingham in 1995. Dr. Kaslow's areas of expertise include infectious diseases, epidemiology, and HIV disease progression and determinants, particularly host susceptibility factors.

Robert S. Klein, M.D., is an attending physician, Division of Infectious Diseases, Department of Medicine, Montefiore Medical Center, and Professor of Medicine, Epidemiology, and Social Medicine at the Albert Einstein College of Medicine, New York City. Dr. Klein received his M.D. from Harvard Medical School in 1971. He completed a residency in Internal Medicine at The Mount Sinai Hospital, New York City, and a fellowship in Infectious Disease at Albert Einstein College of Medicine and is board certified in Internal Medicine and Infectious Diseases. Dr. Klein's areas of expertise include epidemiology, social medicine, HIV and drug use, and HIV disease progression among women.

Marie Laga, M.D., Ph.D., is Head of the Epidemiology and Intervention Section, Department of Microbiology, Center for AIDS and STD, Institute of Tropical Medicine, Antwerp. Dr. Laga received her M.D. from the Catholic University of Louvain, Belgium, in 1982, a M.Sc. in Epidemiology from the London School of Hygiene and Tropical Medicine in 1987, and her Ph.D. in Epidemiology from the University of Antwerp, Belgium, in 1990. Her research has focused on reproductive tract infections and their impact on the health of women in the Third World; female prostitutes facing the AIDS epidemic in Europe and Africa; the epidemiology and interaction of the HIV epidemic with epidemics of other sexually transmitted infections; the development and evaluation of vaginal microbicidal agents; and the organization and integration of public health programs for the prevention and control of STD/HIV in developing countries.

Michelle Murrain, Ph.D., is Associate Professor of Neurobiology, School of Natural Sciences, Hampshire College, Amherst, Massachusetts. Dr. Murrain received her Ph.D. in Biology from Case Western Reserve University in 1987, completed a postdoctoral fellowship at Colorado State University, and received graduate training in Epidemiology and Public Health at the University of Massachusetts, Amherst. She is currently the Acting Dean of Multicultural Affairs, Hampshire College. Her research has focused on studies of opportunistic infections in women with AIDS; the role of poverty in survival with AIDS among women and people of color; and the extent to which race and class determine health status. She has been recognized for her work in community advocacy for women and AIDS issues. Dr. Murrain's areas of expertise include neurobiology; epidemiology; and gender, poverty, and race in HIV/AIDS.

Nancy Padian, Ph.D., is Associate Adjunct Professor and Assistant Chief of Research, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco. Dr. Padian received her Masters in Public Health in 1983 from the University of California-Berkeley School of Public Health and her Ph.D. in Epidemiology from the same institution in 1987. Her research has focused on heterosexual transmission of HIV, pelvic inflammatory disease, and barrier contraceptive use. Dr. Padian has conducted the largest and longest running study of the heterosexual transmission of HIV in the United States. She recently served on the National Academy of Science Panel on Needle Exchange and Bleach Distribution.

John Phair, M.D., is Professor of Medicine, Chief of Infectious Diseases, and Director of the Comprehensive AIDS Center, Northwestern University Medical School, Chicago. Dr. Phair received his M.D. from the University of Cincinnati in 1960 and completed a residency in Internal Medicine and a fellowship in Immunology and Infectious Disease at Yale New Haven

Medical Center. Between 1962 and 1964, Dr. Phair served on the Atomic Bomb Casualty Commission, Hiroshima, Japan. Dr. Phair's clinical research is focused on the natural history of HIV in homosexual men, the immunopathogenesis of HIV disease, and therapy of HIV infection and its complications.

Steven G. Self, Ph.D., is Head of Biostatistics, Division of Public Health Sciences, Fred Hutchinson Cancer Center, Seattle; Professor of Biostatistics, University of Washington School of Public Health; and Adjunct Professor of Biostatistics, The Johns Hopkins University School of Hygiene and Public Health. Dr. Self received his Ph.D. in Biostatistics from the University of Washington, Seattle, in 1981. His research focuses on statistical support and methodology of Phase III efficacy trials of HIV vaccine candidates and other promising prevention methods, and the development of new statistical methods for the design, conduct, and analysis of epidemiologic studies and disease prevention studies.

Sten Vermund, M.D., Ph.D., is Professor and Chair of the Department of Epidemiology, School of Public Health; Professor and Director of the Division of Geographic Medicine, Department of Medicine; and Professor of Pediatrics, School of Medicine, University of Alabama at Birmingham. Dr. Vermund received his M.D. from the Albert Einstein College of Medicine, New York, in 1977; M.Sc in Community Health in Developing Countries from the London School of Hygiene and Tropical Medicine in 1981; Diploma in Public Health from the Royal Institute of Public Health and Hygiene in 1981; and Ph.D. in Epidemiology from Columbia University in 1990. He is board certified in Preventive Medicine and Pediatrics. Prior to joining the University of Alabama at Birmingham, Dr. Vermund was Chief of the Vaccine Trials and Epidemiology Branch, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Dr. Vermund's research has focused on perinatal transmission of HIV, cervical human papillomavirus infection, HIV-associated cervical dysplasia, HIV disease progression in women and men, and preparations for HIV vaccine efficacy trials.

Robert Wood, M.D., is AIDS Control Officer and Medical Director of the AIDS Control Program, Seattle-King County AIDS Project; Associate Professor of Medicine, School of Medicine; and Adjunct Associate Professor of Health Services, School of Public Health and Community Medicine, University of Washington, Seattle. He serves as an attending physician in the AIDS Clinic, Harborview Medical Center, Seattle. Dr. Wood received his M.D. from the University of Rochester in 1970 and completed a residency in Internal Medicine at Dartmouth-Hitchcock Hospital, Department of Medicine. In addition, he studied as an American Cancer Society Fellow at Cambridge University, England. Dr. Wood's research focuses on the study of changes in knowledge, behavior, attitudes, and intentions concerning AIDS among high-risk persons (especially gay and bisexual men and injection drug users), the impacts of interventions designed to limit HIV spread, and direction of HIV/AIDS prevention programs.

Appendix B

Acknowledgments

The Natural History, Epidemiology, and Prevention Research Area Review Panel would like to thank the people listed below who, through interviews, presentations, conversations, and the submission of written materials, provided information important for our work. Affiliations are those at the time of contact.

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