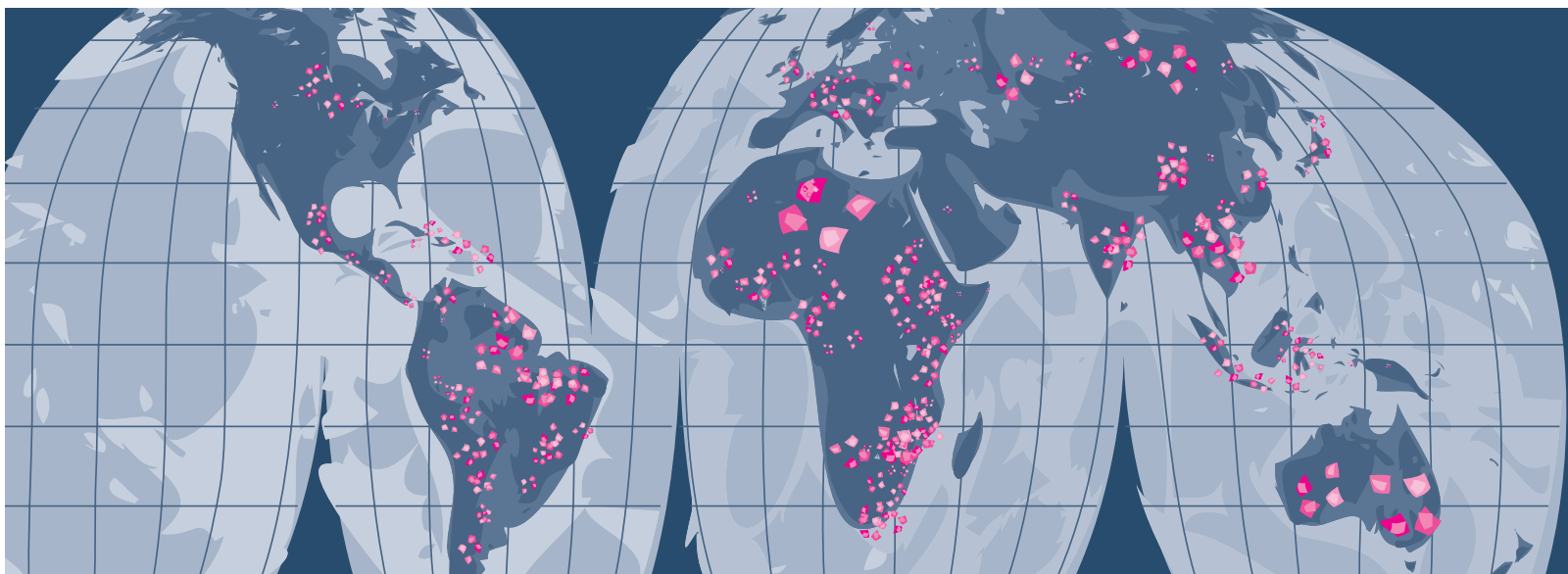


Global AIDS Research Initiative and Strategic Plan



National Institutes of Health

PREPARED BY

Office of AIDS Research, National Institutes of Health

Global AIDS Research Initiative and Strategic Plan

**PREPARED BY
OFFICE OF AIDS RESEARCH, NATIONAL INSTITUTES OF HEALTH**

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Foreword

Foreword

The Office of AIDS Research (OAR) is pleased to provide this document that describes and affirms the global AIDS research commitment of the National Institutes of Health (NIH). Included here are an overview of our extensive international AIDS research and training projects; descriptions of the major international efforts of the NIH Institutes and Centers and the OAR; and the strategic plan setting forth the scientific priorities for this critical research agenda.

By every definition, AIDS is the great plague of the 20th century. The impact of AIDS on developing nations, Asia, Latin America, the Caribbean, and many former Soviet Union countries is staggering, with even greater potential disaster to come. As a growing threat to global security, AIDS is reversing decades of progress in public health and significantly affecting international economies. The cost in lost productivity and profitability, sickness and death, and a significant reduction in the skilled workforce in developing countries will have economic effects worldwide.

Research to address the global pandemic is essential. Since the early days of the epidemic, NIH has supported research efforts in countries impacted by HIV/AIDS. Beginning in 1984 with a research project in Haiti and the establishment of *Projet SIDA* in 1985 in what was then Zaire, NIH has maintained a strong international research portfolio. NIH has expanded this effort to encompass more than 50 countries in Africa, Asia, Europe, and Latin America. The development of research infrastructure, including training of scientists and health care providers, is an essential component of these NIH research programs.

In recent months, critical attention has been brought to the international dimension of the AIDS epidemic, catalyzing efforts across the Government to address AIDS globally. In January 2000, the United Nations Security Council declared that AIDS represents a new kind of threat to economic, social, and political stability and thus is an issue of national security. To address the increasing urgency of the pandemic, NIH is further expanding its commitment to research pursuing interventions that can be implemented in resource- and infrastructure-deprived nations.

To set the scientific priorities for that research, the OAR convened a group of experts with experience in international settings, including those from academia and industry, as well as community representatives. They worked in a collaborative process with scientific and program staff of the NIH Institutes and Centers to develop a strategic plan for international AIDS research. The plan is provided in this document and is based on the most compelling scientific priorities that will lead to better therapies and prevention strategies for HIV infection and AIDS. The OAR is mandated by Congress to develop an annual comprehensive NIH AIDS research plan and budget. The international research agenda will now be incorporated in the overall annual plan, representing an integral and critical component of the NIH scientific agenda.

It is our sincere hope that the fruits of this research will help to alleviate the suffering caused by HIV and AIDS throughout the world.



Jack Whitescarver, Ph.D.
Acting Director
Office of AIDS Research
December 1, 2000

Countries Where NIH Supports AIDS Research Activities

COUNTRIES WHERE NIH SUPPORTS AIDS RESEARCH ACTIVITIES**AFRICA**

Botswana
Burkina Faso
Cameroon
Central African Rep.
Congo
Cote d'Ivoire
Eritrea
Ethiopia
Gabon
Gambia
Ghana
Kenya
Lesotho
Malawi
Mozambique
Namibia
Nigeria
Republic of Guinea
Rwanda
Senegal
South Africa
Sudan
Swaziland
Tanzania
Uganda
Zambia
Zimbabwe

ASIA/WESTERN PACIFIC

Australia
Bangladesh
Kampuchea (Cambodia)
China
India
Indonesia
Japan
Laos
Malaysia
Mongolia
Myanmar (Burma)
Nepal

Pakistan
Philippines
Singapore
Sri Lanka
Taiwan
Thailand
Vietnam

EASTERN EUROPE

Armenia
Belarus
Czech Republic
Estonia
Georgia
Hungary
Latvia
Lithuania
Poland
Romania
Russia
Serbia
Slovak Republic
Slovenia
Ukraine

THE AMERICAS

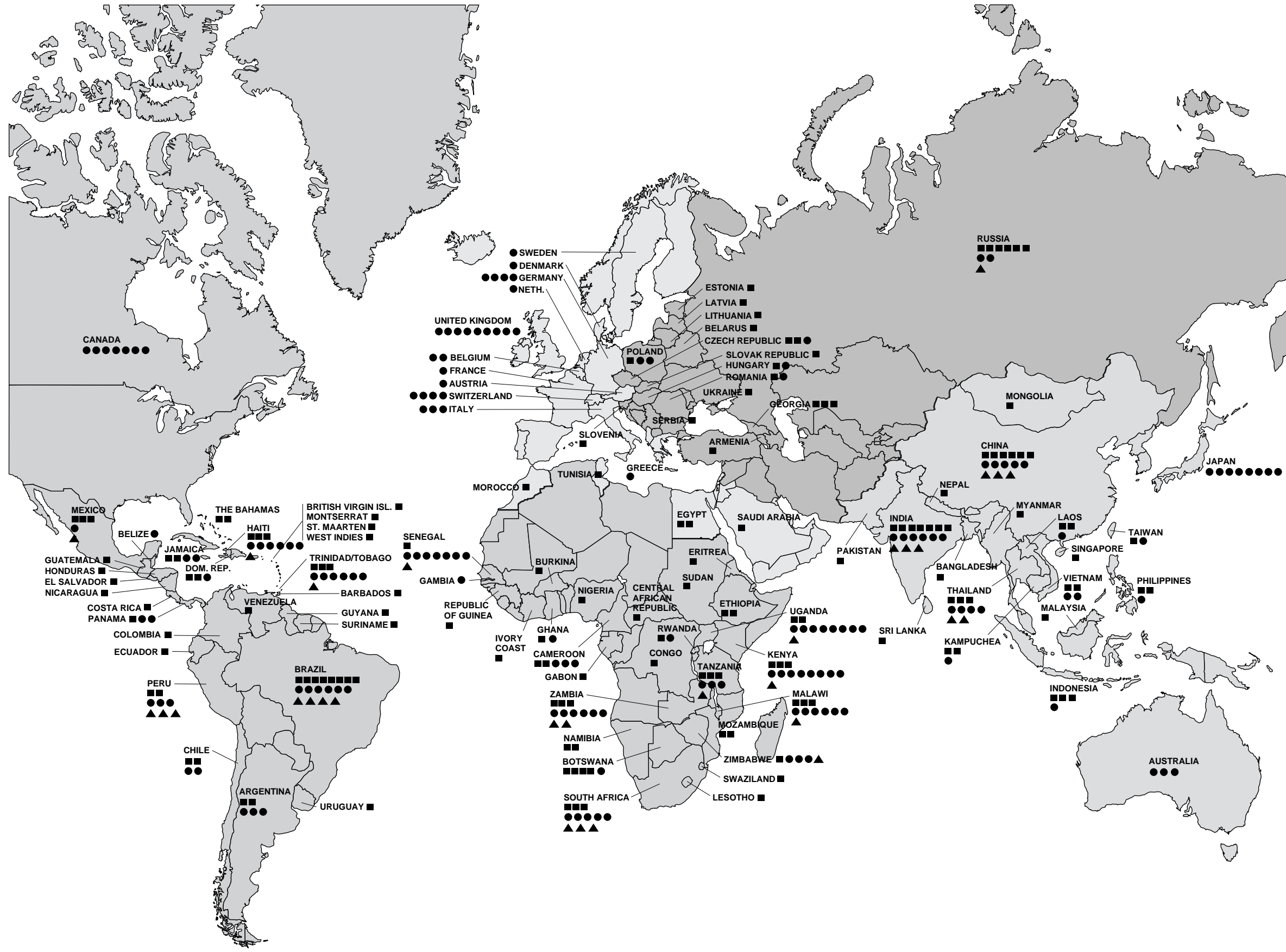
Argentina
Bahamas
Barbados
Belize
British Virgin Islands
Brazil
Canada
Chile
Colombia
Costa Rica
Dominican Republic
Ecuador
El Salvador
Guatemala
Guyana
Haiti
Honduras

Jamaica
Mexico
Montserrat
Nicaragua
Panama
Peru
St. Maarten
Suriname
Trinidad/Tobago
Uruguay
Venezuela
West Indies

**WESTERN EUROPE/
MIDDLE EAST**

Austria
Belgium
Denmark
Egypt
France
Germany
Greece
Italy
Morocco
Netherlands
Saudi Arabia
Sweden
Switzerland
Tunisia
United Kingdom

Location Map of International AIDS Activities



AFRICA
(Total Sites = 108)



- Training Programs (44)
- Research Studies (53)
- ▲ Other Sites* (11)

WESTERN EUROPE/MIDDLE EAST
(Total Sites = 33)



- Training Programs (5)
- Research Studies (28)
- ▲ Other Sites* (0)

EASTERN EUROPE
(Total Sites = 31)



- Training Programs (23)
- Research Studies (7)
- ▲ Other Sites* (1)

ASIA/WESTERN PACIFIC
(Total Sites = 77)



- Training Programs (36)
- Research Studies (33)
- ▲ Other Sites* (8)

THE AMERICAS
(Total Sites = 96)



- Training Programs (46)
- Research Studies (40)
- ▲ Other Sites* (10)

*Other Sites:
Centers for AIDS Research (CFAR),
Mental Health Centers (MH Centers),
Prevention Trials Network (PTN), and
Vaccine Trials Network (VTN).

NIH Commitment to
International AIDS Research

NIH Commitment to International AIDS Research

The National Institutes of Health (NIH) represents the largest single public investment in AIDS research in the world. It supports a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated opportunistic infections and malignancies. Half of the total \$2 billion NIH AIDS research budget supports basic research that benefits all HIV- infected individuals, including those in developing countries. Of the remaining half, NIH conducts and supports AIDS research that has important specific international benefits. Some of this research is taking place in international research sites.

The conduct of research is a critical component of a comprehensive strategy to improve the international response to HIV. Even resource-poor nations can make long-term commitments to participate in research, through collaboration with partners in industrialized nations.

NIH collaborates with the Joint United Nations Programme on AIDS (UNAIDS), host country governments, and in-country scientists in prevention research and preparation for efficacy trials. As part of the Vaccine Trials Network and the Prevention Trials Networks, sites have been established in Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe, China, India, Thailand, Brazil, Haiti, Peru, Trinidad, and Russia. Other active research collaborations are ongoing in these and more than 15 additional developing countries.

INTERNATIONAL RESEARCH AREAS

NIH will significantly increase its investments in this area in FY 2001. The major areas of the NIH AIDS research program of benefit to the international community include:

- **Vaccine Research**
- **Development of Topical Microbicides**
- **Prevention of Disease Transmission and Disease Progression**
- **Research on Women and AIDS**
- **Prevention and Treatment of HIV Infection in Children**
- **Prevention and Treatment of Opportunistic Infections, including Tuberculosis**
- **Capacity Building and Training of Foreign Scientists**
- **Research Collaboration**

VACCINE RESEARCH

- The toll of the epidemic in developing countries where therapeutic and prevention interventions are unavailable or unaffordable, as well as in industrialized parts of the world, dictates the important emphasis on vaccine development.
- NIH spending for AIDS vaccine research has increased by more than 100 percent since FY 1995.
- **President’s Vaccine Initiative:** The President has made the discovery of an AIDS vaccine a national research priority. A safe and effective vaccine is the critical missing element in our armamentarium for the prevention of HIV and ultimate control of the pandemic, and remains one of the highest research priorities. A new Vaccine Research Center has been established at NIH.
- **G-8 Initiative:** At the Summit meetings of the G-8 nations for the past several years, we have agreed to work to devote appropriate resources to the quest for an AIDS vaccine. NIH has also pledged to work with other G-8 nations on vaccine research efforts.
- In recognition of the need to develop vaccines that are efficacious against a variety of strains found around the world, NIH supports studies analyzing genetic and antigenic variation of HIV and targeted toward eliciting cross-reactive immune responses.

**DEVELOPMENT OF
TOPICAL
MICROBICIDES**

- Vaccine Clinical Trials:
 - ▶ To date, more than 60 trials with 30 different vaccine candidates and adjuvants have been conducted worldwide.
 - ▶ To conduct clinical research on vaccines for HIV/AIDS, the NIH supports the HIV Vaccine Trials Network (HVTN), a domestic and international network of sites. The HVTN will carry out a comprehensive program of research to identify an effective and safe vaccine to prevent HIV/AIDS by studying the safety, immunogenicity and efficacy of candidate HIV vaccines, both domestically and internationally. Directly and through collaborations with other investigators worldwide, the HVTN also will support related laboratory research, including the clinical relevance of global viral and host genetic variation and their role in vaccine development. The HVTN is currently identifying the cohorts of populations at risk for HIV infection and building the infrastructure necessary to conduct large-scale efficacy trials of potential HIV vaccine candidates when they become available. These efforts involve strengthening in-country research capacity in developing country sites noted above.
- The changes that have been implemented in this area over the past few years, and the scientific advances that have been achieved, have enormous potential significance, not only for AIDS but for other diseases as well, as progress made in the development of an AIDS vaccine will certainly have implications for vaccines against other life-threatening illnesses.
- The development of safe, effective, and acceptable topical microbicides is a global need to protect women around the world from sexual transmission of HIV infection. The Secretary and the Congress have made this a high priority for U.S. Government-supported research.
- NIH sponsors a comprehensive biomedical and behavioral program for the discovery, development, preclinical testing, and clinical evaluation of topical microbicides and other female-controlled barrier methods for prevention of HIV transmission.
- NIH plans to expand its Topical Microbicide Program Projects involving multidisciplinary research to develop and test new agents and will expand contracts and grants for developing and testing spermicidal and non-spermicidal microbicides and other female-controlled barrier methods.

**PREVENTION
OF DISEASE
TRANSMISSION
AND DISEASE
PROGRESSION**

- With the support of the Congress, the Office of AIDS Research (OAR) is leading an effort to develop a comprehensive NIH Plan for Microbicide Research and Development, drawing on the expertise of academic scientists, representatives from private industry, scientists and care-givers from developing countries, program staff from NIH and other Government agencies, and members of the advocacy community.
- NIH-sponsored programs target studies on factors related to transmission of HIV and the pathogenic mechanisms associated with HIV disease progression through a number of studies in Africa, Asia, and Latin America. These studies focus on the biologic determinants of infectiousness and susceptibility.
- NIH sponsors an extensive biomedical and behavioral research program for the discovery, development, preclinical testing, and clinical evaluation of interventions to prevent HIV transmission, slow disease progression, and limit disease mortality. These intervention programs include the development of topical microbicides and other barrier methods, sexual and drug-using behavioral interventions, strategies to reduce perinatal transmission, and prevention of sexually transmitted diseases (STDs).
- The Prevention Trials Network is designed to conduct research on promising and innovative biomedical/behavioral strategies for the prevention or reduction of HIV transmission among at risk adult and infant populations. The research will include: (1) evaluation of a broad range of interventions designed to reduce adult and perinatal transmission of HIV; (2) basic laboratory studies that address viral and host factors related to risk of transmission, mechanisms of transmission and/or modes of action of successful prevention strategies; and (3) testing of microbicides. The network includes sites in developing nations mentioned above.
- Blood safety: In FY 2001, NIH will initiate a new program targeting the development and evaluation of effective, low cost, and reliable assay systems and inactivation processes to improve the safety of blood supplies in low resource, developing countries.

**RESEARCH ON
WOMEN AND AIDS**

- A number of studies specifically examine complications of HIV disease that are unique to or more prevalent in women than in men. A critical area of concern is the impact of HIV on cervical cancer, as co-infection with human papilloma virus (HPV) is common in HIV-infected women. For example, a study in Africa is examining the natural history of cervical neoplasia in women infected with HIV-1 and HIV-1 and the role of HPV as a risk factor.
- An NIH multi-site international trial is investigating whether women who use hormonal contraceptives are at increased risk for sexual acquisition of HIV. Other studies are planned to examine the possible effects of hormones on infectiousness and disease progression.

**PREVENTION
AND TREATMENT
OF HIV
INFECTION IN
CHILDREN**

- Preventing transmission from HIV-infected mother to child is a priority of NIH intervention research. Initiation of treatment with zidovudine prior to birth, during delivery, and to the infant has significantly reduced the incidence of maternal-fetal HIV transmission in the United States. However, this protocol is not easily applied in developing countries because of cost factors and lack of health care infrastructure. Simpler and less expensive antiretroviral regimens for interruption of vertical transmission are being tested by NIH.
- To reduce transmission further, NIH research is pursuing studies to better understand the timing, mechanisms, and risk factors of perinatal transmission; whether specific strains are more likely transmitted; and the role of co-infection and other factors.
- Nevirapine Study: Clinical findings from an NIH trial in Uganda demonstrated that a single oral dose of nevirapine at the onset of labor to the HIV-infected woman and a single dose of oral nevirapine to her infant within 72 hours of birth reduced the risk of maternal-infant HIV transmission by nearly 50 percent. This simplified, low-cost regimen (\$4) has significant international implications, since it may be a viable way of decreasing perinatal transmission in developing nations.
- Breast Feeding: A recent NIH-sponsored study showed that risk of HIV transmission through breast feeding is highest during the first few months of life. This finding and other ongoing studies will provide important information on the timing, risk factors, and potential approaches to block this mode of HIV transmission.

**PREVENTION AND
TREATMENT OF
OPPORTUNISTIC
INFECTIONS,
INCLUDING
TUBERCULOSIS**

- Caesarean Sections: While initial studies have demonstrated the potential benefits of caesarean sections in reducing the risk of perinatal transmission, further studies are needed to assess the benefits against the risk of these surgical procedures on the infected woman and the potential applicability of this procedure in developing nations.
- Tuberculosis (TB) represents the most common human infection in the world and is the attributable cause of one-third of all adult deaths in developing nations. HIV infection confers the greatest known risk for the development of TB, both the reactivation of latent infection and progression to primary disease, and UNAIDS estimates that approximately 30 percent of all AIDS deaths result directly from tuberculosis. Particularly ominous is the emergence of multidrug resistance.
- In collaboration with the government of Uganda and the Centers for Disease Control and Prevention (CDC), NIH has made significant progress toward practical and affordable prevention measures to reduce the burden of tuberculosis. NIH-supported scientists in Thailand are studying risk factors for infection with *Penicillium marneffeii*, a newly described fungal infection that is the major opportunistic infection (OI) in Thailand and potentially in other Asian nations.

**CAPACITY
BUILDING AND
TRAINING OF
FOREIGN
SCIENTISTS**

- It is critical to the success of international studies that foreign scientists be full and equal partners in the design and conduct of collaborative studies and that they have full responsibility for the conduct of studies in-country.
- To help build capacity in developing countries, the NIH funds the AIDS International Training and Research Program (AITRP). The AITRP provides research training to foreign scientists through grants to United States universities. The program has provided training in the United States for scientists from developing countries in Africa, Asia, and Latin America, and training courses have been conducted in 60 countries. Pilot studies will be launched in FY 2000 to reduce HIV transmission through improving the blood supply in developing nations.
- NIH-supported HIV-related research helps to build laboratory capacity in developing countries where the research is conducted through purchase of laboratory equipment and transfer of research technology.

**RESEARCH
COLLABORATION**

- The translation of research results into effective prevention programs and improved patient care is a high priority. NIH is continuing efforts to assure that research results relate to the cultural, social, and economic contexts of developing countries.
- NIH has established the International AIDS Research Collaborating Committee. The goal of the Committee is to assist in (1) enhancing and promoting international collaboration in HIV research; (2) developing a coordinated international HIV research effort, including biomedical, behavioral, and social science studies; and (3) providing a forum for international exchange. Its membership includes the NIH, other Government agencies and departments that conduct and support international research on HIV/AIDS, agencies involved in the implementation and dissemination of the results of such research, and international organizations such as UNAIDS and the World Bank.
- The development of international collaborations for tracking the natural history and epidemiology of infectious diseases and for obtaining and identifying variants of infectious agents from different geographic regions helped expedite research on AIDS. This experience, and the collaborations established, will be of great value as new epidemic diseases emerge in the future.

NIH International AIDS Research Activities

Office of AIDS Research

Since its inception, the Office of AIDS Research (OAR) has established a number of initiatives to increase and enhance the NIH global AIDS research agenda and development of research collaborations. These include: facilitating international research partnerships and training; disseminating research results; and funding international research projects. OAR supports international workshops to identify research gaps and priorities, share scientific information, and disseminate research advances. OAR provides funding to research projects proposed by the NIH Institutes that address important international AIDS research priorities, including projects targeted to development, implementation, and evaluation of HIV prevention interventions for resource-poor nations.

**INTERNATIONAL
CONFERENCES TO
ENHANCE THE
GLOBAL AIDS
RESEARCH
AGENDA AND
DEVELOP
RESEARCH
COLLABORATIONS**

Vaccines Against AIDS: Innovations and Progress Workshop

September 1999

In collaboration with the Medical Research Council of the United Kingdom, the OAR supported this workshop to address a key area of concern identified by the Summit of the Industrial Nations (G-8). This workshop provided an international forum for scientists from countries funding AIDS vaccine research and development to share scientific information and further develop the research agenda for this important effort.

Conferences on Global Strategies for the Prevention of HIV Transmission from Mothers to Infants

While great progress has been made on research in this field, the challenge is to bring the benefits of these advances to resource-poor nations of the world. The OAR sponsored these international conferences of experts from around the world to help identify remaining research gaps, to disseminate the results of research, and to identify operational research needs that will provide information to help policy makers and organizations implement programs in their countries.

International Conference on Emerging Infectious Diseases in the Pacific Rim

January 2000

The OAR collaborated with the National Institute of Allergy and Infectious Diseases (NIAID), the Government of Japan, and the Indian Council of Medical Research to sponsor the 5th International Conference on Emerging Infectious Diseases in the Pacific Rim, held in Chennai, India. Under the auspices of the U.S.-Japan Cooperative Medical Science Program, the objective of the meeting was to discuss scientific approaches to address HIV/AIDS, tuberculosis (TB), and leprosy in the region. Nearly 200 scientists from 17 countries met to identify these research priorities. During this same time, a Joint Statement was signed between India and the United States regarding Indo-U.S. Collaboration on Prevention of Sexually Transmitted Diseases and HIV/AIDS. This agreement will provide a framework for U.S. and Indian scientists to collaboratively pursue research activities identified during the conference.

International Microbicides Conference

March 2000

The OAR sponsored the first international conference on microbicide research in collaboration with other U.S. and international organizations. The goal of the Microbicides 2000 Conference was to encourage international collaboration among clinicians, researchers, educators, and activists across the disciplines of basic, clinical, and behavioral science and public health. A particular focus of the conference was the need to develop a product that will be easily accessible and acceptable in developing countries. OAR also supported a scholarship program to ensure participation from developing countries. More than 600 participants from more than 40 nations attended.

U.S.-Japan Cooperative Medical Sciences Program: AIDS Panels

OAR serves as the secretariat for the AIDS Panels of the U.S.-Japan Cooperative Medical Sciences Program. These Panels meet each year, providing an opportunity for leading scientists from both countries to present new research findings and to develop collaborative research projects. Through this program, the United States and Japan have pursued research to address needs identified at the summits of the G-8 nations, including accelerated vaccine research and development efforts. These efforts also support the U.S.-Japan Common Agenda, under which the nations have agreed to use bilateral programs to address the AIDS crisis in the developing world.

U.S.-Russia Workshop: Building and Sustaining Cooperation in Emerging and Re-emerging Infectious Diseases Biomedical Research

May 2000

The OAR, in collaboration with NIH Institutes and Centers (ICs), sponsored a U.S.-Russia workshop to build on and sustain research partnerships. The workshop brought together scientists who had received funding from the U.S. Civilian Research and Development Foundation (CDRF) for the Independent States of the Former Soviet Union to conduct research on HIV/AIDS, TB, hepatitis, and other emerging or re-emerging infectious diseases. The objectives of the workshop were to provide a forum for discussion of ongoing research, research findings, and future research directions; to foster the development of networks within the Former Soviet Union for research and research training; and to assist U.S.-Russia partnerships in the identification of potential NIH funding sources.

International Summit Meetings on Immune Correlates of Protection

Defining immune correlates of protection is an essential step in the development of vaccines for HIV. Consistent with the NIH research priorities and agreement among the G-8 nations to increase vaccine research and development, the OAR collaborates with European colleagues to sponsor these meetings annually to discuss the current state of knowledge and research gaps.

**INTERNATIONAL
TRAINING AND
INFORMATION
DISSEMINATION****Immunology, Virologic, and Morphologic Monitoring of HIV Vaccine Trials Meeting***September 2000*

OAR collaborated with the Institute for Tropical Medicine in Hamburg, Germany, to sponsor a workshop on scientific issues related to clinical trials in humans of vaccines for HIV/AIDS. Topics ranged from genetics of vaccines to assessment of immune response.

Training Workshop for Community-Based Health Care Workers in Africa*June 1999*

OAR sponsored a workshop in Nairobi, Kenya, in collaboration with the Global Strategies for HIV Prevention and the Pediatric AIDS Foundation, for health care workers in Kenya, Tanzania and Uganda. Other partners in this workshop included the University of Nairobi, the Eastern Deanery (a 14-parish group of counselors, nurses, and social workers who care for HIV/AIDS patients and their families), the Kenya AIDS Non-governmental Organization Consortium, and the Nyumbani Orphanage. The goal was to provide regional health care workers with research information on prevention of perinatal infection; the vulnerability of women to infection; treatment of sexually transmitted diseases; psycho-social factors in HIV transmission; nutritional interventions; plans for an AIDS vaccine trial in Kenya; the relationship of health care facilities and home care; legal and ethical issues; and access to information. Participants developed plans for implementation in their own work settings. OAR also supported follow-up visits to assess and assist in this implementation.

Caribbean-Wide Training and Information Dissemination Conference*February 2000*

OAR developed this conference in collaboration with Dr. Donna Christian-Christensen, the U.S. Congressional Representative for the U.S. Virgin Islands; health care professionals; and community representatives in the U.S. Virgin Islands. This Caribbean-wide conference was designed to disseminate research results and information on HIV treatment, prevention, and other issues. The 2-day conference took place in five sites: St. Thomas, U.S. Virgin Islands; Barbados; Trinidad; Jamaica; and the Bahamas. Morning plenary sessions were broadcast by satellite from St. Thomas to each of the four additional islands; afternoon sessions were devoted to island-specific issues. Topics ranged from prenatal care and prevention of perinatal transmission to cultural considerations in prevention, treatment, and care. More than 2,300 participants attended, including health care professionals and community representatives.

International AIDS Conferences

The International AIDS Conferences are essential opportunities for scientists, health care providers, policy makers, and community representatives to discuss the latest scientific information. For each of these conferences since 1990, OAR has provided essential support for the organization of the conference and for scholarships to allow attendance of scientists from developing countries.

Information Dissemination in South Africa

November 2000

In collaboration with the Treatment Action Group, OAR is sponsoring conferences in Durban, Johannesburg, and Cape Town, South Africa, to increase understanding among community representatives about basic and clinical AIDS research and to build foundations for recruitment into future clinical trials.

Training and Information Dissemination in China

December 2000

China is initiating its first HIV therapeutic clinical trials. To assist in this effort, OAR supported a workshop to train physicians in the use of virologic and immunologic testing of HIV-infected individuals receiving highly active antiretroviral therapy (HAART). A limited number of physicians and nurses in China are trained in this area. The workshop was designed to allow the Chinese National Center for AIDS Prevention and Control to train physicians and nurses who will then be skilled to train personnel in six provinces in China where trials will be conducted.

FUNDING FOR INTERNATIONAL RESEARCH PROJECTS

Social Desirability Effects on Self-Reports of Behavior (NICHD)

PI.: Mick Couper, University of Michigan

This project will test and validate two alternative computer-assisted methods of collecting self-report data on sensitive topics. Specifically, it will compare computer assisted self-interviewing (CASI) and A-CASI technologies against interview administered data, to test the hypothesis that these privacy-enhancing technologies will increase the truthfulness of self-reports. This project addresses the growing interest in the use of these methods in developing countries, where under-reporting of sensitive behaviors is a concern. It also addresses a priority in the NIH Plan related to the development of methodological research.

Nevirapine + Zidovudine: Prevention of Perinatal HIV in Thailand (NICHD)

PI.: Marc Lallemant, Harvard University

This study will evaluate the efficacy, safety, and tolerance of a single dose of nevirapine (NVP) given to women at the onset of labor and to their infant 48 to 72 hours after birth, in addition to the current Thai ZVD prophylaxis regimen. It will also examine the respective roles of the maternal and the infant NVP and further explore the physiopathology and timing of vertical HIV transmission, co-factors of transmission, clinical status, mode of delivery, viral load, and NVP and ZVD resistance related mutations. The study is a Phase III, double-blind, randomized placebo-controlled trial that will build on an existing collaboration among Harvard University, IRD-France, the Ministry of Public Health of the Kingdom of Thailand, and Mahidol and Chiang Mai Universities.

Older Africans and the HIV/AIDS Nexus (NIA)

PI.: Ed Dowd, WHO (supplement to interagency agreement)

This project will provide quantitative, baseline data on AIDS, aging, and caregiving for long-term monitoring and data collection in a larger Aging in Africa/MDS Project. This project addresses an area of extreme importance in Africa: the impact of HIV/AIDS on older Africans who bear much of the burden of the AIDS epidemic and who must care for sick adult children and orphaned grandchildren. The investigators are working with established community based projects, as well as with UNAIDS and USAID.

Demographic Impacts of the HIV/AIDS Epidemic in Africa (NIA)

PI.: Jane Menken, University of Colorado

Funds are provided to support a Center to develop an experimental program in population aging in Africa that will include: the effects of HIV/AIDS on the elderly, children, and the family; the impact of intervention programs; the effects of migration on the elderly; better estimation of HIV incidence and prevalence; and the impact of population pressure on livelihoods and lifestyles. The Center will take advantage of existing ties with the African Center for Population in South Africa and the Gwembe Tonga Research Project in Zambia and selected sites of INDEPTH (an international network of demographers). The Center will focus on much-needed longitudinal data collection in South Africa and Zambia that will augment cross-sectional census data.

The HIV/AIDS Epidemic, Kin Relations, Household Organization and the Elderly (NIA)**PI.: Albert Palloni, University of Wisconsin**

This project will update a 10-year old data using new procedures to project the impact of the HIV/AIDS epidemic on families, household organization, and the elderly in Sub-Saharan Africa. It will fine-tune a projection model developed in the 1980s by the P.I., by blending micro and macro approaches and utilizing existing population and household survey data collected in-country. This project extends a collaboration with researchers at the University of Natal in South Africa, and will help build capacity in RSA for demographic research on HIV/AIDS.

INDEPTH Longitudinal Data Analysis Workshops in Africa (NIA)**PI.: Jane Menken, University of Colorado**

This project is to develop and conduct two longitudinal data analysis workshops (a year apart) for a network of 24 demographic and health surveillance field sites that include Africa, Asia, and developing areas of Europe and the Middle East (INDEPTH network). The goal is to increase local capacity to collect and analyze data to improve the monitoring of HIV/AIDS in developing countries.

Sociodemographic Impact of AIDS on Older Persons (NIA)**PI.s: John Knodel, University of Michigan, and Mark Van Landingham, Tulane University**

The overall goal of this project is to understand how the HIV/AIDS epidemic directly and indirectly affects older persons in a developing country setting—in this case, Thailand. The investigators will analyze both existing and new data, collected through interviews, focus groups, and surveys among local volunteers, older men, health station staff, etc. The study will triangulate data from a number of sources to provide useful information to Thai policy makers.

International Research on HIV Among Injection Drug Users (NIDA)**PI.: Don Des Jarlais, Beth Israel Medical Center**

This project has three important components, all of which address international HIV prevention issues as well as a priority in the NIH Plan to improve methodological research. These components are: (1) comparative analyses of North American and Russian syringe exchange programs; (2) comparative analysis of data from the second round of the WHO multi-site study of AIDS and drug use; and (3) special follow-up data collection at selected WHO study sites (e.g., Lagos, Nigeria).

**HIV VACCINE
TRIALS
NETWORK**

National Institute of Allergy and Infectious Diseases

In June 2000, the National Institute of Allergy and Infectious Diseases (NIAID) announced the formation of the new international HIV Vaccine Trials Network (HVTN). The HVTN provides a comprehensive, clinically based network to develop and test preventive HIV vaccines. In addition to the nine units based in the United States, participating sites are located in sub-Saharan Africa (South Africa), Asia (China, India, Thailand), Latin America (Peru, Brazil), and the Caribbean (Trinidad, Haiti).

First-year costs for the VTN are over \$29 million. The organization's clinical trials sites are coordinated by a Leadership Group that includes a Core Operations Center at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, which provides administrative, technical and operational support and is led by Lawrence Corey, M.D.; a Statistical and Data Management Center, led by Steve Self, Ph.D., also at the FHCRC; and a Central Laboratory led by Kent Weinhold, Ph.D., at Duke University.

The HVTN builds on the work and organization of the activities of the AIDS Vaccine Evaluation Group (AVEG), which carried out early-stage testing of vaccine candidates, and the HIV Network for Prevention Trials (HIVNET), which conducted domestic and international trials of HIV vaccine and other prevention strategies.

The HVTN will conduct all phases of clinical trials, from evaluating candidate vaccines for safety and the ability to stimulate immune responses, to testing vaccine efficacy. The network's web of U.S.-based units integrated with sites around the globe will allow the HVTN to expand rapidly to carry out larger scale studies of suitable vaccines.

Some of the vaccine candidates and approaches that will be explored include:

- Recombinant viral-vectored vaccines (now in Phase I and Phase II trials), which use non- HIV viruses that are engineered to carry genes with one or more HIV proteins
- Subunit vaccines, which use some protein components of the HIV virus, particularly the envelope protein
- DNA vaccines, made from harmless genes of HIV

**HIV PREVENTION
TRIALS NETWORK**

- A combination of approaches, such as a canarypox vector given with a subunit vaccine or a DNA vaccine
- Other new viral-vectored vaccines, such as a non-disease causing Venezuelan equine encephalitis (VEE) virus suitable for humans and a weakened form of vaccinia virus called MVA

In July 2000, NIAID formed the international HIV Prevention Trials Network (HPTN) to develop and test promising non-vaccine strategies to prevent the spread of HIV. The global initiative will explore alternative measures, besides HIV vaccines, that may be able to block or reduce infection with HIV. The HPTN will constitute NIH's largest comprehensive multicenter network dedicated to this task, comprising core operational, data and laboratory centers, as well as research sites located worldwide in Africa (Malawi, South Africa, Tanzania, Uganda, Zambia and Zimbabwe), Asia (China, India and Thailand), Europe (Russia), South America (Peru, Brazil), and the United States.

Along with NIAID, other NIH components co-sponsoring the HPTN include the National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), and the National Institute on Drug Abuse (NIDA).

Funding for the first year of the project totals slightly over \$30 million, including all of the clinical trials sites as well as the Core Group/Operations Center, led by Ward Cates, M.D., M.P.H., of Family Health International in North Carolina's Research Triangle Park; the Central Laboratory, headed by Johns Hopkins University investigator Brooks Jackson, M.D., in Baltimore; and the Statistical and Data Coordinating Center, led by Thomas Fleming, Ph.D., of the FHCRC in Seattle.

HPTN studies will focus on six key areas of prevention research:

- drugs and/or vaccines that are practical and easy to use to prevent mother-to-infant HIV transmission;
- microbicides (substances designed for vaginal or rectal use) to prevent sexual transmission of the virus;
- interventions to reduce behavior that exposes people to HIV;
- programs to check the spread of HIV through reducing intravenous drug abuse;

- measures to control other STDs and thereby decrease the risk of co-infection with HIV;
- antiretroviral therapy that may protect high-risk uninfected adults who are exposed to HIV, as well as emergency therapy to treat victims of sexual assault.

HPTN researchers will conduct clinical trials of a broad array of promising interventions for HIV, alone and in combination. In addition, HPTN scientists will explore fundamental questions about the virus and factors related to the risk and mechanics of HIV infection in the context of testing promising intervention strategies.

Previously, NIAID's HIV prevention research program was centered in the HIVNET, made up of domestic and international organizations.

ESPRIT

In September 1999, NIAID awarded the University of Minnesota a cooperative agreement grant to coordinate an international trial investigating the efficacy of interleukin-2 (IL-2) in people infected with HIV. The 5-year Phase 3 trial, which will cost a total of \$43 million, will assess whether intermittent IL-2 treatment delays progression to AIDS and extends survival in individuals at an early stage of HIV disease. Called ESPRIT (Evaluation of Subcutaneous Proleukin® in a Randomized International Trial), the trial involves 210 sites in 18 countries.

It is anticipated that 4,000 study volunteers will be enrolled in the study and followed for 4 years. Enrollment began in March 2000, and to date 124 people have entered the study.

James D. Neaton, Ph.D., from the university's School of Public Health, is the principal investigator on the grant, and Donald I. Abrams, M.D. (San Francisco General Hospital, California) and David A. Cooper, M.D. (University of New South Wales, Sydney, Australia) will co-chair the ESPRIT International Steering Committee. Their collaborators will include investigators in Argentina, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Japan, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Thailand, the United Kingdom, and the United States.

Three regional centers located at the University of New South Wales, The Copenhagen HIV Program (Hvidovre University Hospital, Denmark), and the Medical Research Council Clinical Trials Unit (University College London, United Kingdom) are coordinating regional activities including protocol implementation, training, data collection, and data analyses.

**PEDIATRIC AIDS
CLINICAL TRIALS
GROUP**

Current HIV therapies attack HIV and inhibit viral replication. IL-2, a naturally occurring protein produced by the immune system, stimulates the production of CD4+ T cells. ESPRIT will use recombinant IL-2 (Proleukin®) made by Chiron Corporation (Emeryville, CA) to supplement antiretroviral therapy by acting directly upon the immune system to restore its health.

Previous smaller studies have shown that IL-2, in combination with antiretroviral therapy, can result in substantial and sustained increases in CD4+ T cells in people with HIV infection. The goal of ESPRIT is to determine if these CD4+ T-cell increases correlate with an improvement in the clinical course of the disease. This potential outcome can only be determined through a long- term efficacy trial.

Several studies are either planned or underway in the PACTG that involve international collaboration.

These include:

- PACTG 316 — a Phase III randomized, blinded study of nevirapine for the prevention of maternal-fetal transmission in pregnant HIV-infected women was conducted in several countries in Europe, Brazil, and the Bahamas. The study is no longer enrolling but blinded follow-up of the women continues. It is anticipated that the analysis of the data will be completed by early next year.
- PACTG 247 — a randomized, double-blind, controlled study of an increased caloric density infant formula and its effect on growth and nutritional status in HIV-infected infants. The study is ongoing in the United States, and plans are underway to begin enrollment in Brazil in the next several months.
- PACTG 390 is a study to evaluate what treatment regimen to start with and when to switch therapies. It is a strategy/patient management protocol that will be conducted in collaboration with the Pediatric European Network for the Treatment of AIDS (PENTA). The study is not yet open to enrollment.
- The PACTG has recently reviewed applications for international collaborations. Studies will be pursued for the purposes of scientific exchange, enrichment and optimization of resource usage, and to address questions of relevance for both resource rich and resource poor nations.

**ADULT AIDS
CLINICAL TRIALS
GROUP**

Several studies are either planned or underway in the AACTG that involve international collaboration.

- ACTG 384 is a study being conducted in the United States and Italy with a sample size of approximately 900. The study is designed to determine whether the initial use of two nucleoside reverse transcriptase inhibitors (NRTIs) + nelfinavir (NFV) followed by a different two NRTIs + efavirenz (EFV) is superior to the initial use of two NRTIs + EFV followed by a different two NRTIs + NFV. The study will also determine whether initial use of two NRTIs + NFV + EFV is superior to either of the two consecutive three-drug regimens listed.
- ACTG 388 is a comparison of EFV or NFV in combination with Combivir and Indinavir versus Combivir and Indinavir alone (i.e., 4 vs. 4 vs. 3 drugs) in subjects with limited or no prior antiretroviral therapy and ≤ 200 CD4 cells or RNA $\geq 80,000$ copies. It has enrolled 517 subjects and is being conducted in the United States and Italy.
- ACTG 5015 is a Phase II exploratory study examining immunologic and virologic indices in two age-differentiated cohorts of HIV-infected patients to explore the basis of accelerated HIV-disease progression associated with aging. The study is being conducted in the United States, Canada, and Italy.

**ACUTE
INFECTION AND
EARLY DISEASE
RESEARCH
PROGRAM**

Several sites funded through the Acute Infection and Early Disease Research Program (AIEDRP) are collaborating with researchers in other countries.

- Dr. George Shaw at the University of Alabama is conducting a study in Zambia on acute infection and heterosexual transmission of HIV, using patient samples that were previously collected in a discordant couple cohort study.
- Dr. Lawrence Corey at the University of Washington is conducting a study in Australia to study the effects of combination antiretroviral therapy in acute HIV infection with emphasis on immunological responses.

**VACCINE DESIGN
AND
DEVELOPMENT
TEAMS**

In June 2000, NIAID announced four novel public-private partnerships to accelerate development of promising HIV/AIDS vaccines for use around the world. The new partnerships, called HIV Vaccine Design and Development Teams (HVDDT), tap the different skills and talents of private industry and academic research centers, and provide financial incentive to move strong HIV/AIDS vaccine candidates out of the laboratory and into human testing.

NIAID has committed to spend approximately \$70 million over the next 5 years on the four HVDDT contracts that have been awarded.

The HVDDT program encourages pharmaceutical companies to invest more in AIDS vaccine research by partially offsetting their financial risk. HVDDT awards are incentive-based contracts aimed at vaccine candidates in the middle of the development pipeline—those not yet in clinical testing. Applicants had to describe a clear development plan, including timelines to indicate when different phases would be completed. Funding will be provided in increments as these preset milestones are reached. This goal-based incentive structure will help ensure continuous progress toward a testable vaccine while at the same time rewarding companies for research accomplishments made along the way.

Each of the initial HVDDT contracts proposes using a DNA-based HIV vaccine for the initial immunization. The proposals differ in the unique properties of the DNA, the specific immune response that is targeted, the delivery system used, and the manner of boosting the initial vaccine. Each of the proposed vaccines contains the genetic information to make specific HIV proteins, either from the outer viral envelope or the internal viral core, to induce an immune response. The vaccines do not contain enough genetic information to construct a complete virus, and therefore will pose no threat of HIV infection to study participants. The four research organizations that have received an award are listed below:

- *Advanced BioScience Laboratories, Inc.* (ABL), Kensington, MD, Phillip Markham, Ph.D., working in conjunction with researchers at the University of Massachusetts Medical School
- *Chiron Corporation*, Emeryville, CA, Susan Barnett, Ph.D.
- *University of New South Wales*, Australia, David Cooper, M.D., working with a consortium of Australian universities and research organizations
- *Wyeth Lederle Vaccines and Nutrition*, Pearl River, NY, John Eldridge, Ph.D., working with researchers at the University of Pennsylvania and Duke University

**HLA TYPING AND
EPILOPE MAPPING
TO GUIDE HIV
VACCINE DESIGN**

This initiative will support the immunogenetic characterization of selected HIV-infected and uninfected populations and establish a database of human leukocyte antigens (HLA) types and associated T-cell epitopes to guide HIV vaccine design/development. Selected seronegative populations will include those “at-risk” for HIV infection who might be eligible for vaccine efficacy trials at potential NIAID-sponsored domestic and international vaccine trial sites. Selected seropositive populations will include HIV-infected individuals with relatively uncompromised immune systems at NIAID-sponsored domestic and international sites.

In total, it is anticipated that 1,200 individuals (seropositive and seronegative) will be molecularly typed for HLA. The initial emphasis will be on class I typing because of the current interest in cytotoxic T-lymphocyte (CTL)-inducing vaccines. In addition, approximately 150 individuals infected with HIV-1 subtypes B (non-Caucasian populations), A, C, and D (populations in Africa and India) and E (Asian populations) will be studied also to detect and map commonly recognized HIV T-cell epitopes. Samples from seropositive individuals will be shipped to a contractor(s) to be tested for CTL and antigen-specific proliferation, as well as for mapping of HIV epitopes recognized. As currently conceived, a central laboratory would perform the HLA typing while multiple laboratories could conduct the epitope mapping.

The purpose of this new initiative is to: (1) perform molecular HLA typing and T-cell epitope mapping; (2) extend the capabilities of the HIV sequence database to include the analysis of the data (generated by 1), and (3) establish and disseminate a database of this information to the scientific community.

This database will be directly linked to the NIAID-sponsored HIV sequence database. In addition, new and existing HLA molecular typing and T-cell epitope data that is generated through NIAID-sponsored VTN and PTN networks, and other Division of AIDS (DAIDS)-funded research will be centralized and incorporated with data generated through this initiative. The ultimate goal of the project is to develop a comprehensive national and international database that includes detailed HIV-relevant immunogenetic, immunologic, and virologic information that could be analyzed and applied to the design and development of new HIV vaccines.

**LARGE
PROGRAM
GRANTS****Host Virus Interactions During Acute Infection in Trinidad****K. Weinhold****Duke University**

This program grant is dedicated to a comprehensive analysis of primary HIV infection in a unique study group from a highly endemic area of HIV transmission in Trinidad. The principal features of this cohort include large size, absence of bias for symptomatology, frequent sampling, long-term follow-up for clinical endpoints, and appropriately matched control subjects. The general aims of the study are (1) to establish relationships between early symptomatology and disease progression, (2) to provide a much finer resolution of the kinetic of HIV replication through frequent sampling, and (3) to correlate a comprehensive range of host responses with viral replication. The ultimate goal of the program is to identify host responses that are most effective in suppressing HIV replication or in clearing the infection as well as those that are conducive to HIV dissemination and ultimately pathogenesis. Such information is likely to be important for design of preventive and therapeutic strategies that employ host defense mechanisms. The program is composed of four highly interactive projects led by experienced investigators that are tightly connected to a central Clinical Core.

Prevention of Maternal to Infant HIV Transmission in India**R. Bollinger****Johns Hopkins University**

A randomized clinical trial of maternal-fetal HIV transmission is proposed that will directly compare the efficacy of azidothymidine (zidovudine or AZT) alone with AZT + 3TC in 1,200 HIV-infected Indian women enrolled over a period of 24 months. In addition, the effect of length of therapy will also be assessed: more than 40 percent of this cohort will be enrolled after 36 weeks of gestation and 30 percent will be enrolled when they present in labor. This study will also compare the rates of post-partum maternal viral AZT resistance and the morbidity and mortality of mother/infant pairs in the two treatment arms. In addition, this study will characterize factors that promote women's participation in clinical trials to assist future trials, as well as implementation of clinical and behavioral HIV prevention interventions. This study will provide an opportunity to identify and design future interventions and could more rapidly focus resources on specific causes of postpartum morbidity and mortality for mothers and infants in developing countries.

**COMPREHENSIVE
INTERNATIONAL
PROGRAMS IN
RESEARCH ON
AIDS (2002)**

Adjunct Vitamin A Therapy for TB and HIV/AIDS in Malawi

R. Semba

Johns Hopkins University

The objective of the study is to determine whether daily Vitamin A supplementation, given concurrently with tuberculosis (TB) chemotherapy, will reduce mortality in adults with HIV and TB. The investigator proposes to conduct a randomized, double-masked, placebo-controlled clinical trial of daily Vitamin A therapy for 1,100 HIV-infected adults with pulmonary TB in Zomba, Malawi, a population with a high prevalence of HIV and TB. The mortality rate is 45 percent by 24 months in these adults with HIV and TB who have undergone TB chemotherapy. Adults will receive standard TB chemotherapy (isoniazid, rifampicin, streptomycin, pyrazinamide) for the first 2 months, followed by isoniazid and ethambutol for the following 6 months) and adjunct Vitamin A or placebo therapy at the same time. Participants will be followed for vital events for 24 months after enrollment. If adjunct Vitamin A therapy is shown to reduce mortality in adults with HIV and TB, this intervention would have one of the highest cost-benefit ratios known, because adjunct Vitamin A therapy would cost about 80 cents per person and could be readily incorporated with TB chemotherapy.

The CIPRA initiative will provide long-term support for fundamental laboratory and clinical studies that are necessary to lay the foundation for research on practical and affordable methods for prevention and treatment of HIV/AIDS in international settings, especially in developing regions. This research infrastructure will enhance the capability and capacity of host country institutions to conduct relevant research, to prepare for and participate in large-scale HIV vaccine and prevention clinical trials, and to study diagnostic and treatment interventions in local populations.

The large-scale HIV vaccine and prevention trials will be supported through the HVTN, the HPTN, and other organizations. Examples of HIV/AIDS research that may be supported through CIPRA include studies on:

- Incidence, prevalence, modes of HIV transmission, and characteristics of circulating subtypes of HIV in population groups including women, children and adolescents;
- Characterization of the course of early HIV infection and coincident infections in populations likely to be candidates for HIV vaccine and prevention trials;

- Characterization of the CTL epitopes of circulating HIV and their host HLA restriction in populations proposed for clinical trials;
- Characterization of neutralizing antibodies and their reactivity to circulating subtypes of HIV;
- Feasibility of implementation and assessment of sustainable therapeutic interventions within the socio/cultural environment;
- Evaluation of practical diagnostic and interventional regimens for the management of disease in adults and children who are or who become infected with HIV.

Host country leadership will be required to ensure the long-term success of a CIPRA. Research support facilities and projects will be proposed and organized at the initiative of host country investigators. Researchers in some countries may already be sufficiently prepared to initiate independent research programs with CIPRA resources. Others with less developed research capability or infrastructure may require initial assistance and interaction with U.S. institutions to develop their programs. In any case, applicants will be permitted to develop collaborations with U.S.-based institutions; the CIPRA initiative is flexible in the types of arrangements that can be supported to meet these goals.

The program will be coordinated with other international HIV/AIDS research programs sponsored by NIAID, the Fogarty International Center (FIC), NICHD, NIMH, NIDA, the Centers for Disease Control and Prevention (CDC), USAID, International AIDS Vaccine Initiative (IAVI), and the Joint United Nations Programme on AIDS (UNAIDS). Support of specialized training for CIPRA investigators will be coordinated through the AIDS International Training and Research Program (AITRP).

Fogarty International Center

**NETWORKS OF
INTERNATIONAL
RESEARCH
TRAINING
SUPPORTED
BY FIC**

Under the AITRP, scientists primarily from developing countries receive training in research that helps to address the global HIV/AIDS and related TB epidemics. AITRP helps to: (1) establish critical biomedical and behavioral science expertise in developing countries affected by HIV/AIDS and TB; (2) facilitate new prevention research efforts that supplement or complement NIH and other U.S. AIDS and TB research; (3) establish long-term cooperative relationships between U.S. and foreign research groups; and (4) support cooperation between U.S. academic research centers and foreign scientists.

Types of training supported under AITRP include:

- Training that may lead to a M.S. or Ph.D. degree for individuals with previous research experience in biomedical and behavioral HIV/AIDS-related prevention and related TB research disciplines. Duration of training is estimated from 2 to 4 years. Academic courses are taken in the United States. Research could be conducted in the United States but is encouraged to take place in the trainees' home country.
- Training (generally 2 years in duration) in biomedical and behavioral HIV/AIDS-related prevention and related TB research disciplines, which may lead to a M.S. degree for individuals without prior research experience. Academic courses are taken in the United States; research would ordinarily be conducted in the trainees' home country.
- Postdoctoral research experiences (generally 2 years in duration) for foreign health scientists (in the United States) and for U.S. health scientists overseas.
- Training of approximately 3 to 6 months duration conducted in the United States in laboratory procedures and research techniques in support of specific HIV/AIDS prevention and related TB research (for example, development of pilot biomedical and behavioral studies). The training is for individuals with M.S. or Ph.D. degrees.
- In-country, practical and applied short-term training (up to 3 weeks) in support of HIV/AIDS prevention and related TB research for professionals, technicians and allied health professionals, including training to support local participation in institutional review boards (research ethics committees), data and safety monitoring boards, and community advisory boards.
- Advanced research training (approximately 1 to 2 years in duration) for current and/or former trainees, including re-entry grants for in-country prevention research projects such as interventions to prevent the further spread of HIV/AIDS and to prevent and treat TB.
- Support to enable U.S. faculty to be involved in advanced research training activities conducted in-country.
- Support to enable new and minority U.S. health science students (including medical students and residents) to receive overseas health research experiences (generally of 3 to 12 months duration).

Trainees are individuals involved in or expected to be involved in HIV/AIDS prevention and related TB research activities upon completion of training in their home country. The following categories of individuals are eligible for training:

- Foreign health professionals (M.D., D.D.S./D.M.D., Ph.D., or equivalent);
- Foreign professionals with a bachelor's or master's degree in a basic or health science;
- Medical technicians and health care workers;
- Allied health professionals such as behavioral scientists, nurses, nurse midwives, and social workers;
- Current or former AITRP trainees involved in advanced research training in their home countries; and
- U.S. health science students, medical residents and postdoctoral researchers (participating in collaborative research and research training with foreign colleagues).

AIDS International Training and Research Program (AITRP)

Major Collaborating Countries and Principal Investigators

<i>Country</i>	<i>Institution</i>	<i>Principle Investigator</i>
Armenia	SUNY	Dr. Jack A. DeHovitz
Baltics	SUNY	Dr. Jack A. DeHovitz
Bangladesh	Alabama	Dr. Sten H. Vermund
Barbados	Maryland	Dr. William A. Blattner
Botswana	Columbia	Dr. Salim S. Abdool Karim
	Harvard	Dr. Max Essex
	Berkeley	Dr. Arthur L. Reingold
Brazil	Cornell	Dr. Warren D. Johnson
	Hopkins	Dr. Chris Beyrer
	Berkeley	Dr. Arthur L. Reingold

AIDS International Training and Research Program (AITRP)

<i>Country</i>	<i>Institution</i>	<i>Principle Investigator</i>
Brazil (cont.)	UCLA	Dr. John L. Fahey
	Maryland	Dr. William A. Blattner
	Miami	Dr. Gail Shor-Posner
	Miami	Dr. Gwendolyn B. Scott
	Pittsburgh	Dr. Lee H. Harrison
Cambodia	UCLA	Dr. Roger Detels
Cameroon	North Carolina	Dr. Adaora A. Adimora
China	UCLA	Dr. Roger Detels
	UCLA	Dr. John L. Fahey
	North Carolina	Dr. Adaora A. Adimora
Colombia	Miami	Dr. Gail Shor-Posner
Cote d'Ivoire	Berkeley	Dr. Arthur L. Reingold
Czech Republic	SUNY	Dr. Jack A. DeHovitz
Dominican Rep.	Hopkins	Dr. Chris Beyrer
	Miami	Dr. Gail Shor-Posner
Ethiopia	Hopkins	Dr. Chris Beyrer
Georgia	Emory	Dr. Carlos del Rio
	SUNY	Dr. Jack A. DeHovitz
Haiti	Cornell	Dr. Warren D. Johnson
	Hopkins	Dr. Chris Beyrer
	Miami	Dr. Gwendolyn B. Scott
Honduras	Miami	Dr. Gail Shor-Posner
Hungary	SUNY	Dr. Jack A. DeHovitz

AIDS International Training and Research Program (AITRP)

<i>Country</i>	<i>Institution</i>	<i>Principle Investigator</i>
India	Hopkins	Dr. Chris Beyrer
	UCLA	Dr. Roger Detels
	UCLA	Dr. John L. Fahey
Indonesia	Brown	Dr. Kenneth Mayer
Jamaica	Maryland	Dr. William A. Blattner
Kenya	Washington	Dr. Joan Kreiss
Malawi	Hopkins	Dr. Chris Beyrer
	North Carolina	Dr. Adaora A. Adimora
Malaysia	Hopkins	Dr. Chris Beyrer
Mexico	Emory	Dr. Carlos del Rio
	UCLA	Dr. Roger Detels
	UCLA	Dr. John L. Fahey
Mongolia	Alabama	Dr. Sten H. Vermund
Mozambique	Washington	Dr. Joan Kreiss
Myanmar	UCLA	Dr. Roger Detels
Namibia	Columbia	Dr. Salim S. Abdool Karim
Pakistan	Alabama	Dr. Sten H. Vermund
Peru	Washington	Dr. Joan Kreiss
Philippines	Brown	Dr. Kenneth Mayer
Poland	SUNY	Dr. Jack A. DeHovitz
Romania	Miami	Dr. Gwendolyn B. Scott
Russia	Yale	Dr. Michael H. Merson
Senegal	Harvard	Dr. Max Essex

AIDS International Training and Research Program (AITRP)

<i>Country</i>	<i>Institution</i>	<i>Principle Investigator</i>
South Africa	Columbia	Dr. Salim S. Abdool Karim
	Hopkins	Dr. Chris Beyrer
Tanzania	Harvard	Dr. Max Essex
Thailand	Harvard	Dr. Max Essex
	Hopkins	Dr. Chris Beyrer
	Berkeley	Dr. Arthur L. Reingold
	UCLA	Dr. John L. Fahey
Washington		Dr. Joan Kreiss
Trinidad/Tobago	Maryland	Dr. William A. Blattner
Uganda	Case Western	Dr. Christopher Whalen
	Hopkins	Dr. Chris Beyrer
Vietnam	Emory	Dr. Carlos del Rio
	Berkeley	Dr. Arthur L. Reingold
	UCLA	Dr. Roger Detels
	UCLA	Dr. John L. Fahey
Zambia	Alabama	Dr. Sten H. Vermund
	Miami	Dr. Gail Shor-Posner
	Miami	Dr. Gwendolyn B. Scott
Zimbabwe	Berkeley	Dr. Arthur L. Reingold

**FIC-PLANNED
ACTIVITIES**

FIC-planned activities related to HIV/AIDS include expansion of AITRP by awarding an expected six new awards in FY 2000; further strengthening of training and research capacity building linked to NIAID VTN/PTN awards; further strengthening of training and research capacity building linked to NIMH Popular Opinion Leaders (POL) awards; expansion of training related to blood safety in collaboration with the National Heart, Lung, and Blood Institute (NHLBI); expansion of training related to AIDS-

associated malignancies in collaboration with the National Cancer Institute (NCI); expansion of training related to oral health manifestations of AIDS in collaboration with the National Institute of Deafness and Other Communication Disorders (NIDCD); expansion of training related to drug abuse and HIV/AIDS in collaboration with NIDA; geographic expansions for training of scientists from China, India, and Africa; expansion of training linked to the Center for AIDS Research (CFAR) program; expansion of a training and research capacity building linked to the future initiatives in collaboration with the National Institute of Nursing Research (NINR) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA); and collaboration with other Institutes and Centers (IC) efforts to build international centers of research excellence related to HIV/AIDS.

National Institute of Mental Health

Prevention remains a critical priority in stopping the AIDS epidemic that is emerging worldwide. Few epidemics are ever cured by treatments, and this certainly is the more expensive route. Behavioral prevention works now and can be mobilized within a community to address the major factors associated with the rapid development of an epidemic. The NIMH has made a commitment to the development of an international HIV/STD prevention program. The bidirectional goals for this program are: (1) extend the generalizability of research findings to international settings; (2) identify assumptions and cultural issues in prevention programs; and (3) understand the situational determinants and dynamics of AIDS prevention in multicultural settings. This report describes the NIMH Collaborative HIV/STD Prevention Trial and research programs being conducted in India and South Africa. Other studies are being conducted in South America, Sub-Saharan Africa, and Russia.

NIMH COLLABORATIVE HIV/STD PREVENTION TRIAL

Because effective individual prevention approaches are not rapid enough to avert the epidemic and because they are too resource intensive, NIMH has initiated this collaborative trial in six countries—China, India, Peru, Russia, Uganda, and Zimbabwe. This trial is adapting the Popular Opinion Leader Model, a community-level behavior change intervention, which has the potential to reach large numbers of people, be cost-effective, and be feasible for implementation even in areas with limited resources.

**RESEARCH
PROGRAM
IN INDIA**

While the Popular Opinion Leader Model (POL)—based on the theory of social diffusion—has been tested in multiple sites with multiple populations in the United States, this intervention engages Community Popular Opinion Leaders (C-POLs) to serve as behavior change agents to friends and neighbors in their community. The intervention is expected to strengthen norms about safer sexual behavior and encourage risk reduction among at-risk populations.

The collaborating institutions conducting this trial are: (1) University of California at Los Angeles and Chinese Academy of Preventive Medicine in Beijing, China; (2) The Johns Hopkins University and YRG Centre for AIDS for Research and Education in Chennai, India; (3) Cayetano Heredia University and University of California at San Francisco working in Lima, Peru; (4) Medical College of Wisconsin and St. Petersburg State University and Biomedical Center in Petersburg, Russia; (5) Columbia University and Makerere University in Rakai, Uganda; and (6) Battelle and University of Zimbabwe.

NIMH has made a major commitment to support behavioral prevention research in India and currently has several projects being conducted by NIMH investigators. Johns Hopkins and YRG Care are one of the six teams implementing the NIMH Collaborative HIV/STD Prevention Trial in Chennai, India. Another study is being conducted of HIV/STD risk behaviors among patrons of wine shops in Chennai.

Investigators at the University of California at Los Angeles and at the Indian Council on Medical Research are conducting a study to identify HIV/STD risk factors for Indian women and developing an intervention that will integrate disease prevention and reproductive health for clinics. This team is also conducting a study of STDs in women.

The first randomized clinical trial of an intervention for women in Calcutta is being conducted by an investigator from the University of California at Los Angeles and the developer of this comprehensive, empowerment AIDS prevention program. Approval was just secured to expand this study to two additional communities in order to generalize the results.

An investigator at the University of Syracuse is collaborating with an investigator at NIMHANS in Bangalore, India. They will adapt and test an HIV/STD prevention program for seriously mentally ill.

Investigators from Yale University are initiating a study of AIDS stigma and HIV/STD prevention in India. Small workshops are planned in Delhi, Mumbai, Calcutta, Chennai, and Bangalore to explore this topic and lay out research questions.

**RESEARCH
PROGRAM IN
SOUTH AFRICA**

NIMH has taken three delegations of researchers to India to develop a collaborative research program with Indian investigators. A fourth workshop is planned for January 2001 in Mumbai.

NIMH-supported investigators at Columbia University have a history of conducting research projects in South Africa. They have concentrated on assessing the acceptability and utility of female-controlled methods for different populations. They have also collaborated with mental health care providers in South Africa to develop and implement HIV prevention programs among people with severe mental illness. One study is currently being done in collaboration with a large public psychiatric institution in KwaZulu/Natal province, which has the highest HIV seroprevalence in rates in South Africa. The goals are to train mental health care providers in South Africa in basic knowledge of HIV/AIDS, communication with patients about sexual issues and stigma, and to develop and adapt HIV preventive interventions for persons with severe mental illness. They are also planning to conduct a seroprevalence study among the mentally ill.

The South African Medical Research Council has invited NIMH to participate in a workshop this fall to develop a collaborative research agenda. Scientists from the United States and South Africa will present data and then develop some collaborative research projects to address some of the emerging HIV/STD prevention needs. The areas of prevention programs for heterosexual men and violence associated with HIV/STD transmission have already been identified as priority areas.

NIMH sponsored an exhibit booth at the XIIIth International AIDS Conference in Durban, South Africa. The theme of the booth was "Behavioral Prevention is Today's AIDS Vaccine!" A mathematical program called NIMH/ASIST (AIDS Strategic Intervention Simulation Tool) that permits modeling the HIV/STD epidemic in developing was previewed. This model is unique because it has a user-friendly interface, models both viral and bacterial STDs, and permits the user to project the impact of specific prevention programs on the seroprevalence and incidence over a 30-year period.

**AIDS
INTERNATIONAL
TRAINING AND
RESEARCH
PROGRAM**

National Cancer Institute

The Division of Cancer Treatment and Diagnosis, NCI, initiated and continued several international activities in AIDS malignancies for FY 2000; they included the following:

- Funded five meritorious FIC AITRP supplements in AIDS malignancies;
- Sponsored and organized the 4th International AIDS Malignancy Conference (IAMC);
- Conducted several AIDS Malignancy Working Group (AMWG) meetings focused on international issues.

The five AITRP supplement applications propose to build training and research capacity in the AIDS-associated malignancy field in resource-poor countries. The AITRP supports HIV/AIDS related international training and research for foreign health scientists, clinicians, and allied health workers from developing countries and emerging democracies. The primary goal of the AITRP is to build biomedical and behavioral research capacity for the prevention of HIV/AIDS and related complications. To achieve these goals, the AITRP facilitates cooperation between U.S. academic research centers and foreign scientists. A summary of the AIDS malignancy funded AITRP projects' objectives follows:

- Foster the development of a Center for Excellence in HHV-8 research in Kenya.
- Build capacity for research and clinical trials in AIDS-associated malignancies (Kaposi's sarcoma and AIDS-related lymphomas) in Uganda.
- Train investigators in the diagnosis, treatment, and prevention of cervical cancer in Uganda.
- Train investigators in the detection, early treatment, and prevention of cervical cancer in India and in evaluating the effects of HIV on human papilloma virus (HPV) acquisition, persistence, and risk for cervical cancer.
- Provide research-training opportunities in AIDS-associated malignancies to enhance the investigators' abilities to conduct research in Brazil.

**INTERNATIONAL
AIDS
MALIGNANCY
CONFERENCE**

The NCI created and sponsored the first National AIDS Malignancy Conference in 1997 and has continued to sponsor this conference annually. Recognizing the international nature of the epidemic and the international representation of attendees, the conference was renamed the IAMC. The 4th IAMC was held on May 16–18, 2000, in Bethesda, MD. The objectives of these conferences are to bring together national and international investigators to showcase progress and stimulate research across diverse disciplines in both basic and clinical research. Topics included malignancies in AIDS, transplantation, and other types of immune deficiencies. The format included invited lecturers, as well as oral and poster presentations of submitted abstracts. To increase public access, highlights from each meeting are provided on the internet, and abstracts and monographs are published.

**AIDS
MALIGNANCY
WORKING
GROUP**

In addition to the large international meeting, in 1996 the NCI created a smaller strategy group, the AMWG, to identify research opportunities, gaps in our knowledge, and suggest ways to address these issues. The AMWG is a multidisciplinary group composed of scientists, clinical investigators, internal NIH staff, and patient representatives. This past year, we focused on international research priorities and identified international NIH initiatives or projects in AIDS with leveraging potential for AIDS malignancy research.

Specific suggestions for AIDS malignancy research in resource-poor countries included the following:

- Provide assistance for cancer registry development.
- Target the Asian population and India, where infrastructure is in place.
- Target cancers that are rare in the United States, for example HHV-8 related primary effusion lymphoma. The prevalence of these cancers may be higher in areas where HHV-8 is more prevalent, such as Africa.
- Investigate the international heterogeneity of cancer and the lifetime risk of developing cancer, including non-AIDS defining cancers and primary gastric lymphoma.
- Encourage and improve communication between NCI and NIAID-funded clinical trials networks in AIDS. Potential benefits include patient referrals to relevant studies and coordination of laboratory studies of mutual interest. Networks of interest include the NCI-funded AIDS Malignancy Consortium and the NIAID-funded AIDS Clinical Trials Group, the HPTN, and the HVTN.

**INTERNATIONAL
HIV/AIDS
RESEARCH AND
TRAINING
PROGRAMS**

National Institute of Child Health and Human Development

Over the last decade, the NICHD has devoted approximately 10 percent of its budget annually to AIDS-related research and training. This program has included basic, clinical, epidemiological, and behavioral research targeting the prevention, natural history, and treatment of AIDS in women, infants, children, and adolescents. Priority research and training activities are supported through peer-reviewed grants and contracts, often in direct cooperation with other NIH ICs, and with extramural research partners. In building this program, NICHD has concentrated on areas of institutional and programmatic strength, including natural history and pathogenesis studies in women and children, preventive and therapeutic clinical trials, behavioral studies to inform prevention and treatment efforts, and the development and evaluation of contraceptive/microbicides.

During the past 3 years, the AIDS pandemic has had an increasing impact on women, infants, and children, particularly in developing countries. The NICHD has responded by significantly expanding its support for international HIV/AIDS research and training. This expansion has included the support of an increasing number of investigator-initiated grants with foreign components, primarily in Sub-Saharan Africa. New clinical research sites in Latin America and the Caribbean have been added to the NICHD Pediatric Perinatal HIV Clinical Trials Network. Support also has been provided for a major multi-site study of the impact of hormonal contraceptives on HIV transmission in Africa and Asia. Grant supplements have been solicited and awarded to academic scientists engaged in behavioral research and training, to allow the expansion of their programs into Africa, India, and Russia. Also, an individual patient data meta-analysis has been undertaken, focused on breast-feeding and other issues of particular importance in developing countries. In addition, in recognition of the impact HIV is having on overall maternal and child health, NICHD has integrated HIV/AIDS research into other priority programs sponsored by the Institute. This includes the new Global Network on Women's and Children's Health Research, established with co-funding from the Bill and Melinda Gates Foundation.

This expansion of NICHD's support for international HIV/AIDS activities has been in direct response to key characteristics of the global epidemic and major unanswered scientific and medical questions within the Institute's mandate and areas of expertise. Promising opportunities to reduce mother-

**INTERNATIONAL
EXPANSION OF
NICHD'S
PEDIATRIC/
PERINATAL HIV
CLINICAL TRIALS
NETWORK**

to-child and heterosexual transmission have emerged from recent research on short-course, inexpensive antiretroviral regimens; factors associated with the reduction of risk in breast-feeding; microbicides; and behavioral interventions and barrier methods that help prevent heterosexual transmission. As some developing countries move toward even more widespread provision of treatment and care for HIV-infected individuals, additional research questions emerge along with the urgent need to better inform clinical practice and health policy decisions.

The NICHD has worked for more than a decade with the NIAID-sponsored PACTG on a research agenda that targets prevention and therapy for HIV and AIDS in mothers, newborns, children, and adolescents. NICHD is expanding its plans and support for the conduct of clinical trials internationally, with special emphasis on the implementation of appropriate trials in midlevel developing countries. With NICHD sponsorship, patients have been enrolled in clinical trials in the Bahamas and at two sites in Brazil. Further expansion will include additional sites in Brazil and possibly other Latin American and Caribbean nations.

**PREVENTION OF
MOTHER-TO-CHILD
TRANSMISSION OF
HIV IN INDIA**

In follow-up to NICHD staff involvement in the January 2000 Indo-U.S. Conference on HIV/STD Prevention Research in Chennai, India, NICHD has initiated a program of clinical research in India to address the prevention of MTCT, by obtaining Government of India approval for such activity. Program and scientific staff from NICHD and its clinical research collaborators planned to travel to India in late September 2000, to meet with representatives of key medical, public health, and research organizations. The primary purpose for these meetings is to discuss the current status of relevant research activities in India, shared research priorities, and best opportunities for cooperation. A joint MTCT research plan will be developed with the Indian National AIDS Control Organization and with the Indian Council of Medical Research, for implementation in early 2001.

**IMPROVED CARE
AND
MANAGEMENT OF
WOMEN,
CHILDREN, AND
ADOLESCENTS
AFFECTED BY HIV
IN SUB-SAHARAN
AFRICA**

In February 2001, NICHD and cooperating NIH ICs will convene a conference in Africa to engage African scientists, health care providers, and policy makers in the development of a research agenda directly relevant to African conditions and needs. The conference will review state-of-the-art research and discuss future research priorities related to the improved care and management of HIV-affected women, infants, children, adolescents, and families. Issues to be addressed will include: growth and metabolism in infected children; reduction of risk factors for MTCT, including breast-feeding; the impact of tropical infectious diseases on HIV pathogenesis

**INTERNATIONAL
RESEARCH AND
TRAINING IN
SOCIAL AND
BEHAVIORAL
SCIENCE**

and transmission; use of anti-retroviral and other therapy and prophylaxis in African settings; standards of care for children, including nutritional interventions; and the involvement of traditional healers, midwives, and others in HIV care and management. These agenda topics have been partially developed through a consultation held in Durban, South Africa on July 19, 2000, and other direct input from African scientists and clinicians. In recognition that this is an under-researched area of work, the results of the workshop will be used to help design a grant solicitation for research of priority in Africa at a time when improved care and management of HIV-affected individuals is of rapidly growing importance.

NICHD has awarded \$1.4 million dollars in FY 2000 to support a range of AIDS-related social and behavioral research projects in Africa and Russia over a 2-year period. These are envisioned as pilot efforts that can lead to expanded training and research cooperation between leading U.S. academic centers and counterpart centers in Africa, India, and Russia where expanded, high-quality behavioral research is a critical need. This is both a research support initiative and a capacity-enhancing activity. Examples of the supported activities in FY 2000 include:

- Collection and analysis of data on AIDS-related knowledge, attitudes, and risk behavior in a cohort from the Russian Longitudinal Survey
- A study of HIV prevalence differentials between urban/rural locations and HIV prevalence among adolescents in Tanzania
- A longitudinal study to assess migration, social, and economic change in families of HIV- infected women and children in Uganda
- Pilot research activities for development of an AIDS intervention to prevent compensated sexual behavior among adolescent girls in Zimbabwe
- A study to promote dual protection behavior among rural South African youth and to develop and test a school-based protection intervention
- A study of HIV risk and preventative behavior among adolescents in the context of rural-urban migration in Nigeria
- Assessment of audio computer-assisted self-interviewing (A-CASI) techniques for reporting of sensitive behaviors related to sexual activity/perception of AIDS and STD history among adolescents in Kenya

**HORMONAL
CONTRACEPTIVES
AND RISK OF HIV
ACQUISITION**

- Analysis of census data to develop timing and development of HIV in Kenya, South Africa, Lesotho, Zambia, The Gambia, and Botswana, and assessment of methods to analyze regional variations of HIV-AIDS-related mortality and examine relationship between socioeconomic status (SES) and mortality.

Hormonal contraceptives are among the most widely used contraceptives globally. Since HIV infection primarily affects women of reproductive age who are making decisions regarding pregnancy and contraception, it is important to conduct studies that will clearly define any elevation in risk of HIV infection that may result from hormonal contraceptives and other factors related to reproductive health. Evidence to date, not sufficient for conclusion, suggests that hormonal contraceptives may substantially increase the risk of HIV infection in women who use hormonal contraceptives over those who do not. NICHD is now in the third year of funding a major international study on the impact of hormonal contraceptives (oral contraceptives and injectables) on the risk of HIV and other factors of significance in the heterosexual transmission of HIV. Over this period, ancillary studies have been added with special funding to make optimal use of the research cohort and data generated in this ambitious study involving 6,400 HIV sero-negative women in a prospective observational study. The ancillary studies address genital shedding, viral fitness/host response, herpes simplex virus, HPV, bacterial vaginosis, and other important factors in developing countries.

**TARGETED
RESEARCH ON STIs
(INCLUDING HIV)
AND RTIs IN INDIA**

In November 2000, the Indo-U.S. Joint Working Group on Contraception and Reproductive Health will sponsor a research agenda-setting workshop in New Delhi, India, on the diagnosis, antecedents, outcomes, prevention, and treatment of sexually transmitted infections (STIs), including HIV, and reproductive tract infections (RTIs). A goal of the workshop is to generate joint research proposals. To facilitate the generation of strong clinical research proposals, NICHD also sponsored a clinical trials training workshop for 35 promising young Indian investigators in March 2000, in Mumbai, India. NICHD, and any other interested ICs, will provide approximately \$.5 million for both the support of the STI/RTI workshop and follow-on grants or grant supplements to support joint research on STI/RTIs. The results from this research will have clear relevance for the prevention of HIV transmission and acquisition in India where co-infections are common and female RTIs, in particular, are poorly investigated or understood.

FY 2001 PLANS**GLOBAL
PARTNERSHIPS FOR
AIDS RESEARCH IN
WOMEN,
CHILDREN, AND
FAMILIES**

In addition to the initiatives described above and significant on-going support for the HPTN and CFAR networks, NICHD plans to support new initiatives to address critical international priorities:

NICHD (and co-sponsoring ICs) plans to support multiple awards to U.S. investigators for the development of HIV/AIDS-related “research centers of excellence.” These grants will support partnerships with foreign researchers and academic/medical institutions in areas where the epidemic is most severe (Africa, Asia including India, and the former Soviet Union) and where less is known about the epidemic but the potential for increasing incidence is large (China, Indonesia, and Malaysia). These will be multidisciplinary awards and will focus on research, capacity building, and training, involving both U.S. and developing country scientists. Through these partnerships, new researchers will be trained in the use of locally available and transferred research tools, techniques, and methods. Basic biomedical, clinical, and behavioral and social science research will be supported. Interventions based on locally relevant findings will be designed, implemented, and evaluated in preparation for large-scale local implementation. Emphasis also will be given to research of special relevance to the prevention of AIDS and HIV transmission/acquisition in women, including research on locally appropriate reproductive health issues, gender-based risk factors, barrier methods, and contraceptive microbicides.

The types of research solicited under this initiative will include:

- Testing and evaluation of culturally appropriate interventions to prevent HIV transmission
- Studies of the impact of HIV on individuals, families, communities, and populations in the developing world
- Biomedical studies focused on prevention of maternal-child transmission of HIV
- Biomedical studies of reproductive health and local factors, which either enhance or diminish the risk of HIV
- Multidisciplinary modalities of treating HIV disease in infected infants, children, youth, and women
- Clinical trials and epidemiologic studies of methods to prevent HIV transmission or acquisition
- Basic behavioral and social science research contributing to the design of effective prevention strategies to reduce the spread of HIV/AIDS in the developing world

**MICROBICIDE
PRECLINICAL
DEVELOPMENT
PROGRAM**

- Basic and intervention research related to voluntary counseling and testing and the care and management of HIV-infected individuals in developing countries

NICHD, with the likely participation of other NIH ICs, will support a program of coordinated P01 grants to conduct research on the pre-clinical development of novel non-vaccine approaches for the prevention of sexual transmission of HIV-1 and for contraception (i.e., novel microbicides with and without contraceptive activity). These grants may involve international cooperation, and it is the stated intent of the program to generate promising new microbicides that can enter domestic and international HIV/STI prevention trials. Active participation with industry will be encouraged to allow that segment of the scientific community to contribute both intellectual and material resources. Maintaining an international perspective about the use of promising microbicides also will be encouraged. The interaction of academic and non-profit research institutions with industry and Government, both domestic and international, will facilitate subsequent development and marketing of any new products that result. The Request for Applications (RFA) for this program was issued in September/October 2000.

**WOMEN'S HIV
PATHOGENESIS
NETWORK**

NICHD also has issued an RFA for establishment of a Women's HIV Pathogenesis Network, designed to fund P01 grants to conduct research on gender-specific biological factors that could have an impact on HIV-1 acquisition, transmission, and disease progression, as well as on the nature of HIV-disease manifestations in women. The program projects will recruit women (domestically and internationally) from diverse racial and ethnic groups, age cohorts, HIV-exposure groups, and lifestyles, and make comparisons wherever possible with male control groups. Research will delineate the underlying mechanisms of action of estrogen, progesterone, and other hormones on HIV replication in the genital tract. Studies also will include research in cohorts of HIV-infected women to assess the effect of natural and exogenous hormonal changes on virologic and immunologic parameters before and during infection, which potentially influence the infectivity of seropositive women for male sexual partners.

**INITIATIVE ON
PEDIATRIC
TUBERCULOSIS**

TB in children is an important cause of morbidity and mortality, globally. Significant gaps exist in our understanding of the pathogenesis and diagnosis of this important public health threat, particularly in countries with high prevalence of HIV/AIDS. It has been estimated that up to one third of the world's population is infected with TB. Childhood tuberculosis is thought to serve as an important potential reservoir of future adult tuberculosis exposure and disease.

In an effort to define a research agenda to begin to address gaps in knowledge about childhood tuberculosis, NICHD, FIC, NIAID, and the International Pediatric Association have initiated discussions to focus attention on the needs and opportunities for biomedical and behavioral research on childhood TB. As a result of these discussions, plans are being developed to convene a research and training agenda-setting conference in 2001, focused on childhood tuberculosis particularly in the developing world. A clear emphasis of this meeting will be the need to develop an integrated approach to TB in children and related conditions, in particular HIV/AIDS. In addition to NIH ICs, it is anticipated that this effort might be of interest to the World Health Organization (WHO), the CDC, USAID, and the World Bank, all of which are heavily involved in adult TB research and control programs. Scientists and research-oriented clinicians from countries with high incidence of childhood TB and HIV also will be enlisted as key participants. In addition to the identification and summarization of current knowledge about childhood TB, a key product of this conference will be the delineation of future priorities, options, and opportunities to advance our understanding of this public health issue.

ORAL ASPECTS OF HIV/AIDS

National Institute of Dental and Craniofacial Research

The National Institute of Dental and Craniofacial Research (NIDCR) is becoming involved in international networks that include a solid oral health/AIDS component. We are working with other Institutes (NCI, NIAID, NICHD) on trans-NIH international initiatives. Understanding the immunology of the oral cavity and all aspects of oral viral transmission are primary objectives.

The NIDCR AIDS program is supporting work on the Epidemiology of Oral HIV 1 and 2 in High Risk Women. A component of this work is being carried out in Africa, through the University of Washington.

The NIDCR AIDS Program is co-funding an award under the FIC-sponsored AITRP.

The NIDCR has supported scholarships for travel to the 4th International Workshop on the Oral Manifestations of HIV Infection, held in South Africa in July 2000. This meeting included a full day of training for the individuals who attended, aimed at increasing their awareness of the

opportunistic infections associated with AIDS. There will be follow-up on the efficacy of this approach. Several individuals from southern countries participated.

National Institute of Neurological Disorders and Stroke

INTERNATIONAL AIDS RESEARCH CONSORTIUM

Several European academic centers were the first to respond with significant research efforts and care for the neurological complications of HIV-1. Clinical studies led the way in evaluating the extent of HIV-1 infection in the brain. Large medical centers in major European cities such as Edinburgh, Amsterdam, and Paris have maintained active AIDS clinical and basic science research efforts with contacts in Western and Central Africa, India, and Asia, which reflects the ethnic and racial diversity in the United States. With increasing understanding of the effectiveness of highly active antiretroviral therapy (HAART) and treatment for non-neurologic complications for AIDS patients in the United States, similar efforts to provide treatment to HIV-1 infected individuals in developing countries, where the epidemic is not in control, should draw closer attention. There is little known about the extent and severity of nervous system involvement in such countries even with international planning to help provide treatment for AIDS. Since it is recognized that HIV-1 infection in the central nervous system (CNS) occurs early after infection and that the brain may serve as a reservoir for multiple strains of HIV-1, as well as 'opportunistic' viruses, much more needs to be learned in this population in order to design and plan truly effective management and treatment of AIDS patients worldwide.

The National Institute of Neurological Disorders and Stroke (NINDS) is working to establish an international consortium of experienced clinical and basic AIDS researchers to examine this problem in greater detail. The Consortium will address issues such as obtaining epidemiologic information on neurological disease in both adults and children. Further evaluation of the rates of occurrence and the effects of therapy where available will help to underscore the need for new initiatives. Some patient cohorts are already in place for such a study, but it will be necessary to establish this information in developing countries. The program will also examine viral strains that are present in the CNS compared with the periphery. Are there neurotropic strains of HIV-1 that can be found in populations generally not treated for

**EXTRAMURAL
PROGRAM
ACTIVITIES**

peripheral infection? Whether clinical trials specific for CNS diseases could be conducted in such situations is uncertain. However, it is known that the major causes of HIV-1 associated encephalopathy is the inflammatory reaction in the brain to infection, release of toxic cytokines, and recruitment of immune system cells into the brain as a result of chemokine synthesis. It may be promising to treat with anti-inflammatory drugs or develop novel ways in which treatment strategies can be used.

Studies involving diverse patient populations suffering from complex, multifactorial disease processes requires a well-organized group effort. An international consortium of investigators with clinical and basic expertise in the areas of neurology, pediatrics, neuropathology, and neurovirology will provide the leadership for this effort.

National Institute on Drug Abuse

Canada

A grant with the University of British Columbia is studying groups of adult injection drug users (IDUs) in Vancouver and Montreal for trends in HIV seroincidence and to identify and explain the reasons why needle accessibility alone is not sufficient to halt HIV infection rates among IDUs. Of particular interest is the impact on IDUs of the type of drug, pattern of drug use, micro-social climate, macro-social climate, and attitudes on HIV incidence. HIV seropositive study participants are offered extensive pre- and post-test counseling and referrals for free medical and psychosocial care. Recent analytical findings indicate that aboriginal people, a significant minority in Canada, were 1.6 times more likely than other drug injectors to seroconvert. This reflects the predilection of HIV to select disadvantaged and minority populations in different countries and settings. Data also indicate that the hepatitis C virus (HCV) positivity rate is approximately 90 percent in the drug-injecting population. In comparing HCV-positive versus HCV-negative IDUs, HCV-positive IDUs were three times more likely to be infected with HIV, more likely to have a history of incarceration, and more likely to have never been in a methadone program.

China

NIDA is funding a project in Guangxi Province, China. This study, in its first year of funding, will document both prevalence and incidence of HIV infection and associated risk factors for infection among drug users. The study will also document the prevalence and distribution of different subtypes of the HIV virus and will determine the virus subtypes in newly

infected drug users and compare the transmissibility of those subtypes in IDUs and their sexual partners. The study will also track changes in risk profiles and viral subtypes over time. The study is directed by Dr. Xiao-Fang Yu, Johns Hopkins University, in collaboration with the Guangxi Health and Anti-epidemic Center and the Chinese Academy of Preventive Medicine.

China/Vietnam

A supplement awarded in September 1999 to the National Development Research Institute, Inc., supports a cross-border HIV prevention project for IDUs and their sexual partners between Yunnan Province, China, and Lao Cai, Vietnam. The Swedish International Development Agency (SIDA) and the Ford Foundation are also contributing financial support to the project. NIDA is supporting the design of the HIV prevention intervention and its evaluation in the project's first (current) year. Work involves site visits to candidate intervention villages and finalization of the intervention and evaluation designs in collaboration with the in-country partners in China and Vietnam. The process of developing and implementing cross-border and multinational HIV prevention projects and strategies for assisting those seeking to develop cross-border collaborative projects will be developed. Researchers also plan to build on findings from this effort to develop an expanded project. This study represents an important research opportunity for research on coordinated programs that might reduce the spread of HIV across national borders in areas of the world in which the HIV epidemic is rapidly increasing among drug injectors.

Russia (five-city research study: Nizhny Novgorod, Pskov, Rostov-Na-Donu, St. Petersburg, and Volgograd)

A supplement awarded to the Beth Israel Medical Center in the summer of 2000 ("National Study of Syringe Exchange Programs") will analyze data from a Russian syringe exchange program. The purpose of the supplement is to extend the basic research question of the parent grant (the effectiveness of HIV prevention programs for IDUs in different communities) from a U.S. national to an international level. This will be accomplished through three steps: (1) comparative analyses of U.S. and Russian syringe exchange programs, (2) comparative analyses of data from the second round of the WHO multi-site study of AIDS and drug use, and (3) special follow-up data collection at selected WHO study sites. HIV has spread among injecting drug users in 114 different countries in the world and is spreading very rapidly in many different areas, with incidence rates of 20/100 person-years at risk or greater. Comparative studies of different HIV prevention programs in different communities are needed to develop a community-level understanding of successful (and unsuccessful) HIV prevention.

The Russian syringe exchange study and the second round WHO multi-site study present unique opportunities for cross-national research on the spread of injecting drug use and on limiting the spread of HIV among injecting drug users. The Russian syringe exchange study has data from over 1,200 IDUs from five Russian cities with syringe exchange programs, and the WHO study will have data from over 4,800 injecting drug users from at least 12 cities. WHO study sites include cities in Asia, Africa, South America, North America, and Europe. The WHO research design includes one round of data collection. This supplement will permit additional data to be collected in up to three sites of special scientific interest. (*NOTE:* One of three sites of special scientific interest site has already been identified—Lagos, Nigeria—where injecting drug use has been rapidly increasing, and interventions are being developed to both address the problems of injecting drug use itself and the spread of HIV among the new IDUs.) Additional data collection in Lagos will thus provide greater understanding of the possibilities for simultaneously addressing the problems of increasing drug injection and the spread of HIV among drug injectors.

Thailand

NIDA is funding a project in Thailand that is investigating the epidemiology of HIV infection among opiate and/or amphetamine users. The project, in its second year, is based in Chiang Mai, in northern Thailand. The project will determine risk factors for infection and will ascertain the contribution of risk factors, such as injection and sexual behaviors and history of STDs, to acquisition of infection. The project will also assess the prevalence and impact of other co-morbid conditions such as TB and hepatitis. HIV viral subtypes circulating among opiate and/or amphetamine users will also be characterized. Analysis of data from the only in-patient drug treatment program in northern Thailand demonstrates high rates of new HIV infection, with the highest rates among opiate injectors, and more recent data indicate a growing problem with amphetamine use in this area. The study is directed by researchers at Johns Hopkins University, in collaboration with Chiang Mai University and the Northern Drug Dependence Treatment Center of the Ministry of Public Health.

Another project funded by NIDA in Thailand is investigating hepatitis C among various populations, including drug users, sex workers, patients with STDs, and military recruits. The project is in its first year of funding and is directed by researchers at Johns Hopkins University, in collaboration with Chiang Mai University. The research will address the epidemiology and transmission of hepatitis C, as well as the virology and natural history of the disease in persons with and without HIV infection.

**GLOBAL RESEARCH
NETWORK ON HIV
PREVENTION IN
DRUG-USING
POPULATIONS**

The Third Annual Meeting of the Global Research Network on HIV Prevention in Drug-Using Populations was held in Durban, South Africa, July 5–7, 2000. The eleven co-sponsoring organizations included NIDA, Health Canada, the Medical Research Council of South Africa, the CDC, the FIC, UNAIDS, the National Department of Health of South Africa, the OAR, U.S. National Institutes of Health, Office of HIV/AIDS Policy (Department of Health and Human Services [DHHS]), the United Nations Office for Drug Control and Crime Prevention, and the WHO.

Approximately 80 researchers and health organization members attended the 2-day closed meeting, with additional people attending on the third and final day, which was open to the public. The meeting provided an opportunity to (1) continue the progress made over the past 2 years by advancing the science of HIV prevention to avert, slow, or stop the rate of spread in drug-using populations in diverse settings around the world; (2) review emerging findings from quantitative and qualitative studies of HIV/AIDS prevention in injection and noninjection drug users; (3) facilitate the global diffusion and application of empirically-based principles on HIV prevention in drug-using populations; (4) enhance opportunities for national, regional, and international collaborations on drug abuse and HIV/AIDS prevention research, with a focus on Africa; and (5) explore other HIV/AIDS and drug abuse-related health conditions and consequences.

As the meeting was held in South Africa to coincide with the International AIDS Conference, an emphasis was placed on the African situation with regard to HIV prevention and drug use. Session topics included a global perspective of HIV prevention research in drug-using populations; an overview of HIV/AIDS in China and Vietnam; research experiences from Africa on HIV and drug use; the role of surveillance in HIV and injection drug use prevention research; social, economic, and political factors associated with changing patterns of drug use and HIV; consequences and implications for prevention; challenges of translating evidence-based HIV prevention research findings into program practice and policy change; dissemination of research findings and capacity building; and future challenges and research priorities. A commentary panel was also held on HIV and drug use prevention research in Africa.

The meeting highlighted an urgent need for a global research network for local, national, and international researchers to share and make accessible science-based knowledge to prevent HIV transmission in drug-using populations.

**COLLABORATION
WITH AIDS
INTERNATIONAL
TRAINING AND
RESEARCH
PROGRAMS**

NIDA contributes support to the following programs and collaborating countries through the Fogarty AITRP.

Program Director	Collaborating Country/Countries
Dr. Salim Abdool Karim Columbia University New York, NY	Botswana, Namibia, South Africa
Dr. Chris Beyrer Johns Hopkins University Baltimore, MD	Brazil, China, Dominican Republic, Ethiopia, Haiti, India, Malawi, Malaysia, South Africa, Thailand, Uganda
Dr. William A. Blattner University of Maryland Baltimore, MD	Barbados, Brazil, Jamaica, Trinidad/Tobago
Dr. Jack DeHovitz State University of New York	Armenia, Baltics, Czech Republic, Georgia, Hungary, Poland
Dr. Roger Detels UCLA Los Angeles, CA	Cambodia, China, India, Mexico, Myanmar, Vietnam
Dr. Michael H. Merson Yale University New Haven, CT	Russia

**HIV NETWORK FOR
PREVENTION
TRIALS**

NIDA also contributes to the HIVNET in support of domestic and international research.

National Heart, Lung, and Blood Institute

**IMPROVING THE
SAFETY OF BLOOD
SUPPLIES IN LOW
RESOURCE,
DEVELOPING
COUNTRIES**

There is an urgent need to establish low-cost, effective strategies to protect the blood supplies from HIV and other blood-borne pathogens in low resource, developing countries. Thus, a demonstration project is proposed to establish low-cost, effective strategies to improve blood safety in such countries. The prevalence of blood-borne pathogens in blood donors from developing countries can be extremely high (e.g., HIV-1 prevalence of 30-

50% in parts of certain African countries). The project would enlist two neighboring, developing countries in which one of the partners would have the necessary resources, blood banking technologies, and expertise to support the less-advanced country. As an example, Zambia and Zimbabwe are blood banking leaders in their respective regions. They could serve as knowledgeable partners to countries in need of help, such as Malawi or Tanzania.

The overall benefit of this program would be a significant improvement in transfusion safety in developing countries. It is important that once the project is completed, the program continue and be self-sustaining. It is more likely to occur in a paired, cooperative setting with resources and technological expertise in relatively close proximity and the likelihood that the partners share some common interests and cultural similarities. When it is demonstrated that this partnering strategy is effective, the program could then be replicated in other developing nations. The citizens of those countries would benefit as well as U.S. citizens who may be visiting or residing in the area and in need of blood transfusion. The program would also provide an infrastructure to test new, low-cost assay systems and procedures. Studies could evaluate the feasibility of testing plasma pools for antibodies to infectious agents. Pool testing would greatly reduce the number of tests needed and the accompanying costs. With the prevalence of HIV-1 and certain other infectious agents so high in donors in developing countries, clinical trials of new inactivation procedures that destroy blood-borne pathogens could be conducted far more rapidly than in the United States. Less resource-intensive strategies might include efforts to recruit safer donors who are at lower risk, such as volunteer donors, repeat donors, female donors, or older age donors. This activity could be conducted through and in collaboration with the FIC.

National Institute on Aging

A complete and accurate vital registration system does not exist in any African nation, and censuses are not adequate to measure the rapid progression of an epidemic like HIV/AIDS. If we are to impact the rate of progression of the epidemic and the steady state prevalence of HIV in large populations, we desperately need to cultivate accurate, agile data collection systems that can provide the kind of rich, timely data necessary to understand the progression of the epidemic and what we might be able to do to limit it. Concurrently, we need to rapidly develop significant local capacity to operate those data collection systems and conduct the primary analysis of the data

WORLD HEALTH ORGANIZATION

that is collected. These data can lead to a highly focused, intervention-oriented research agenda and inform us about the social and economic impact of this pandemic on societies and families.

The National Institute on Aging (NIA) is supporting a number of activities to enhance data infrastructure in a number of developing countries, investments that will facilitate research and prevention of HIV/AIDS.

With partial support from NIA and OAR, the WHO is creating a minimum data set (MDS) with a sustainable data management system to study a number of issues, including the impact of AIDS on older Africans. This project will also supplement ongoing qualitative data collection with quantitative data on the direct and indirect effects of AIDS on older persons at the family level, for the larger Ageing in Africa/MDS Project that involves four partner countries (Ghana, South Africa, the United Republic of Tanzania, and Zimbabwe). National and regional projections can result from these data. The project will also facilitate capacity-enhancing programmes with local researchers, social services, health care providers, and caregivers on the impact of the pandemic on older persons and orphaned children.

INTERNATIONAL NETWORK OF FIELD SITES WITH CONTINUOUS DEMOGRAPHIC EVALUATION OF POPULATIONS AND THEIR HEALTH

Understanding and planning ways to combat the spread and impact of HIV/AIDS requires good data to track not just the disease, but also changes in mortality, fertility, and population age structure and composition. The University of Colorado at Boulder Center for Demography of Health and Aging will conduct a longitudinal data analysis workshop in Africa for a network of demographic and health surveillance field sites, the International Network of field sites with continuous Demographic Evaluation of Populations and Their Health in developing countries (INDEPTH).

INDEPTH is composed of 24 demographic and health surveillance sites in Africa, Asia, and developing areas of Europe and the Middle East. The network has brought similar projects together into a professional organization that aims to improve the quality of the individual projects and more importantly to pool the data coming from the projects and coordinate multi- project research initiatives.

PLANNED ACTIVITIES

- The University of Colorado at Boulder Center for Demography of Health and Aging will initiate a developing and experimental program in population aging that includes the following substantive issues in Africa: the effects of HIV/AIDS on the elderly, children, and the family; the impact of intervention programs; the effects of migration on the

elderly; better estimation of HIV incidence and prevalence; and the impact of population pressure on livelihoods and lifestyles.

The Center will take advantage of already existing strong ties with the African Center for Population in South Africa, the Gwembe Tonga Research Project in Zambia, and selected sites of INDEPTH. Nearly all of the work of the Center will be carried out with African collaborators. The Center will focus on longitudinal data collection in South Africa and in Zambia. These data will augment cross-sectional data that are traditionally collected through censuses and other sources such as that planned in the MDS for Africa project with the WHO.

- The Center for Demography of Health and Aging at the University of Wisconsin will collaborate with a researcher from the University of Natal, South Africa, to study the HIV/AIDS epidemic, kin relations, household organization, and the elderly in sub-Saharan Africa. Important new sources of information have emerged that could be used to investigate the effects of HIV/AIDS on family and household organization and on the transformation of family and residential arrangements of the elderly.

Two interconnected lines of research will be pursued. First, new procedures will be designed for projecting the impact of the epidemic on families, household organization, and the elderly. Second, a number of data sets—including micro samples of census of population and household sample surveys—will be analyzed to empirically assess the transformations and provide benchmarks for fine tuning the models.

- The sociodemographic impact of AIDS on older persons will be studied by researchers at the University of Michigan and Tulane University. The overall goal of this project is to understand how the HIV/AIDS epidemic directly and indirectly affects older persons (aged 50+) in a developing country setting. Despite extensive research on the epidemiology of AIDS, little attention has been given to how older adults are affected by these epidemics, especially for those older persons who may depend upon or become responsible for the care of infected persons and their dependents.

The researchers will both collect new data and build upon research currently in the field in six specific topics: (1) risk behaviors of older persons for HIV acquisition; (2) AIDS-induced migration and its significance for older parents; (3) community reaction to older care givers of persons with AIDS; (4) interactions between health personnel and older persons caring for persons with AIDS; (5) further assessment

of the emotional impact of having a child become sick with and die from AIDS; and (6) assessment of the demographic magnitude of the impact of AIDS on older persons in other affected developing countries. In addition, the project will conduct a comprehensive and critical review of the substantive implications and methodological lessons from their project for promoting an understanding of the impact of AIDS on older populations in other settings in the developing world.

COLLABORATION WITH RUSSIA

National Institute on Alcohol Abuse and Alcoholism

The NIAAA supports international research, education, and training in an effort to further understand the causes, consequences, treatment, and prevention of alcoholism and alcohol-related problems. The NIAAA has established an international collaboration with researchers and medical education specialists in Russia to develop research-based methods for the prevention and treatment of alcohol problems in patients with HIV infection. Unique to this collaboration is the high rate of alcohol consumption in Russia and related health problems, as well as their mandatory HIV testing policy. This collaboration will allow U.S. and Russian investigators to determine (1) the critical elements necessary for effective identification and treatment of alcohol problems in patients with HIV/AIDS, (2) effective treatment strategies of HIV/AIDS for individuals with concomitant alcohol abuse or addiction in the context of differing socioeconomic situations, and (3) effective prevention interventions for those at high risk for HIV infection and substance abuse. The data generated from the ongoing collaborations can be useful in the context of health disparities research in the United States.

The NIAAA supports an education and training collaborative project between the Center for Addiction Research and Education at the University of Wisconsin in Madison and Pavlov Medical Academy in St. Petersburg. The focus of the collaboration for FY2001 will be to develop and test curricula materials for medical school and postgraduate training faculty specialists in addiction medicine, infectious diseases, and primary care. The curriculum units will focus on identifying and treating alcohol problems in HIV/AIDS patients, preventing alcohol problems in HIV/AIDS patients, treating infectious disease in individuals with alcohol problems, medications issues with patients who may be using alcohol during treatment, medications compliance issues, and other topics. An evaluation of training of Russian faculty from a number of appropriate disciplines will allow for testing of the materials.

In addition, the NIAAA supports a research collaboration between Boston University School of Medicine and the Leningrad Regional Dispensary of Narcology. The primary goal of the research is to better understand the relationships among alcohol use, HIV infection, and HIV risk behaviors in Russia. The prevalence of HIV infection is increasing among alcohol-abusing patients in the Leningrad Region as is co-morbidity associated with alcohol addiction. The study will have as a key resource an existing serum bank of samples from 5,000 alcohol-abusing patients in the narcological hospital near St. Petersburg. The study plans to assess alcohol use problems and explore the relationship between alcohol use and HIV risk behaviors. The long-term goal of the project is to determine appropriate prevention interventions to reduce the transmission of HIV infection in Russia.

National Institute of Nursing Research

COLLABORATION WITH AIDS INTERNATIONAL TRAINING AND RESEARCH PROGRAM

In FY 2000, the NINR is participating in the AITRP developed by the FIC. The purpose of this initiative is to train scientists to address the global HIV/AIDS and related TB epidemic through research. AITRP helps to: (1) establish critical biomedical and behavioral science expertise in developing countries affected by HIV/AIDS and TB; (2) facilitate new prevention research efforts that supplement or complement NIH and other U.S. AIDS and TB research; (3) establish long-term cooperative relationships between U.S. and foreign research groups; and (4) support cooperation between U.S. academic research centers and foreign scientists.

PLANNED ACTIVITIES

In FY 2001, the NINR will be participating in the International Initiatives to Prevent HIV/STD Infection with the NIMH. The purpose of this initiative is to scale up HIV/STD prevention programs and policies in developing countries and to find low-resource, cost-effective prevention programs. This initiative will encourage new and expanded collaborative efforts between U.S.-supported researchers and researchers in other nations to test behavioral interventions to stop the spread of HIV infection and its consequences. This initiative will support cooperative relationships between U.S. and foreign research groups to: (1) identify successful interventions for targeted populations, (2) facilitate the conduct of scientifically valid and ethically sound HIV/AIDS prevention research, and (3) develop methods to implement prevention programs for large-scale use.

NIH Strategic Plan for
International AIDS
Research

International Research Priorities

SCIENTIFIC ISSUES

To date, HIV has infected more than 50 million people around the world. Already, AIDS has killed more than 16 million people, surpassing tuberculosis and malaria mortality to become the leading infectious cause of death worldwide, according to recent data released by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). In 1999, a record 2.8 million people died from AIDS—more than in any prior year. New epidemics are rapidly spreading in Russia, Eastern Europe, and Central Asia, and there are now warning signs of newly emerging HIV/AIDS epidemics in the Middle East. UNAIDS estimates that in India, between 3 and 5 million people are now infected, with the number of new infections doubling every 14 months. AIDS remains a serious threat in Latin America: the scope of the epidemics in Central America and the Caribbean is escalating. Africa remains the epicenter of the pandemic, bearing the heaviest burden of disease. Africa has 71 percent of all the people living with AIDS, worldwide; 83 percent of global AIDS deaths; and 95 percent of the world's AIDS orphans.

From a global perspective, the major modes of acquiring HIV infection are heterosexual transmission and transmission by injecting drug users (IDUs). The vast majority of infections occur through heterosexual transmission, and approximately 46 percent of all of the HIV-infected people in the world are women. Because of the high level of HIV infection among women, the potential exists for large numbers of infected children, since infants

**CENTERS OF
EXCELLENCE FOR
INTERNATIONAL
COLLABORATION**

can become infected with HIV, from infected mothers *in utero*, at birth, or during breast-feeding. Mother-to-child transmission accounts for 90 percent of infection among children, worldwide. In the worst-affected countries in the world, between 20 and 45 percent of pregnant women are HIV positive, and one-third of their babies are infected. Injecting drug use is fueling epidemics in Central and Eastern Europe and some countries of Asia; it is also a major concern in industrialized nations and the Middle East. In 1999, the world's most rapidly accelerating epidemic was in the newly independent states of the former Soviet Union, where the proportion of the population living with HIV doubled between end-1997 and end-1999.

The NIH collaborates with UNAIDS, host country governments, and in-country scientists in prevention research and preparation for efficacy trials of various interventions. Significant efforts have been undertaken, particularly with Kenya, Malawi, South Africa, Uganda, Zambia, and Zimbabwe in Africa; Brazil, Haiti, and Trinidad and Tobago in Latin America; and India and Thailand in Asia. In total, NIH-supported research studies are ongoing in approximately 50 countries around the world.

Because more than 90 percent of new infections occur in developing countries, where current therapies are unaffordable and/or undeliverable, it is critical to conduct research that can help address the epidemics in these countries. NIH has long supported a portfolio of international AIDS research, with an emphasis on (1) describing the nature of HIV/AIDS in different geographical regions and (2) developing prevention interventions that can be implemented in resource-poor and infrastructure-deprived settings. These studies have been conducted through collaborative relationships between U.S. and foreign scientists. NIH plans to further enhance its international efforts.

Ethical considerations must be paramount in the development of international collaborations. The fundamental step in addressing ethical considerations, critical to the success of international studies, is to ensure that foreign scientists are full and equal partners in the design and conduct of collaborative studies: they have full responsibility for the conduct of studies in-country. This responsibility should include full participation in the conceptualization of the research; development of protocols; study implementation and collection of data; data processing and analysis; and dissemination of information about the research and its results, through the lay press, professional meetings, and publications in scientific journals. A second step in addressing ethical considerations is to assist developing

countries acquire the internal capability and the capacity to conduct independent ethical and scientific review. Proposed studies must receive full ethical review and approval in the country where the research will be conducted, as well as in the United States, and the studies should fully conform with the ethical principles that prevail in both countries. Finally, study participants and the communities from which they come in host countries must have maximum possible access to any preventive or therapeutic products developed during the course of research. This consideration should be an essential element in the discussion as the research is being developed.

Equally important to an international research effort is the need to expand and sustain laboratory capacity in developing countries, to improve clinical capabilities, and to develop a cadre of trained scientists. These improvements will help ensure that the research conducted is of high quality, will facilitate the transfer of sustainable technologies, and will make it easier to translate the results of the research to the affected populations. Thus, the research effort must focus on strengthening institutions and building capacity, in addition to the biomedical research question under investigation.

PRIORITY FOR FUTURE RESEARCH:

- **Establish centers of excellence in international settings that will provide an environment that promotes the development of true and equal partnerships between U.S. and foreign investigators. These centers will support basic research and long-term cohort studies, serve as loci for studies of efficacy of biomedical and behavioral prevention interventions (including Phase I, II, and III vaccine trials), function as training centers for investigators from throughout the region, and serve as bridges with programs that provide services.**

RESEARCH TO ADDRESS LOCAL EPIDEMICS

To effectively address their epidemics, developing countries need a great deal of information. Research conducted in developing countries provides: (1) information that can be used to establish programs to prevent HIV infection in the community; (2) information relevant to the development of a safe and effective vaccine that can be used for the populations participating in the research; and (3) information useful to providers of health care and other services to help them care for their patients who are infected and to help families and others who are affected by HIV/AIDS.

Prevention of infection in diverse populations, and in diverse settings globally, is of highest concern. Issues of relevance to developing countries include heterosexual transmission; mother-to-child transmission (MCT); transmission

through use of injection drugs; and transmission in health care settings. Strategies are needed to prevent blood-borne transmission in health care settings, including blood screening strategies and technologies and the role (i.e., use/misuse) of transfusion and injections. Also needed are behavioral and other interventions to address the risk of acquiring HIV through injecting drug use.

Since most HIV infection in the world is acquired through sexual transmission, it is critical to develop the best sustainable, behavioral, economic, and environmental interventions for reducing sexual transmission in both men and women. Because of the tremendous cultural diversities found throughout the world, it is not possible to simply transplant interventions developed for one cultural setting to a new one. It is necessary to conduct research to identify the specific cultural and social variables that must be considered so that interventions can be adapted to new settings, and to provide a foundation for the development of new interventions specifically designed for a particular cultural and social context. In this regard, efforts will be targeted toward selected populations at risk, especially adolescents.

Globally, women are at high risk for becoming infected, perhaps because of both biological and socioeconomic factors. It is critical to develop biomedical strategies to prevent heterosexual transmission, with particular emphasis on women, such as microbicides, barrier methods, and syndromic management of sexually transmitted diseases (STDs). To further this effort, it will be necessary to identify the biological determinants of infectiousness and susceptibility in both men and women. Several international cohorts provide unique opportunities for such research. In April 2000, NIH convened a “Biology of Transmission Think Tank” to identify future directions for research in this important area. There are several issues of concern: whether women who use hormonal contraceptives are at increased risk for acquiring HIV infection; the role of the mucosal surface in transmission; the role of viral subtypes in transmission; and the role of STDs in transmission.

There is a global need to develop safe, effective, and acceptable topical microbicides to protect women around the world from sexual transmission of HIV. Currently, 60 microbicide candidates are under development, 23 of which are at the clinical testing stage. To further enhance the microbicide research effort, this year NIH sponsored Microbicides 2000, an international conference with the objectives of (1) establishing a global dialogue to enhance knowledge about microbicides; (2) identifying new research opportunities, including related methodological and behavioral issues; and (3) improving

understanding of the cultural, ethical, and economic obstacles to development and use of a microbicide. With a specific focus on including participants from developing countries, the conference provided researchers and public health workers from diverse regions with an opportunity to gain practical knowledge and to develop international research collaborations.

In addition, some complications of HIV are unique to, or more prevalent in, women than in men. Studies are needed to examine the possible effects of hormones on infectiousness and progression of disease in women. Another question is the impact of HIV on cervical cancer, because co-infection with human papillomavirus (HPV) is common in HIV-infected women. These and other issues are being studied in international cohorts.

Transmission of HIV from infected mother to child has severely affected many developing countries. Initiation of treatment with zidovudine before birth, during delivery, and to the infant has significantly reduced the incidence of MCT in the United States. However, this protocol is not easily applied in most developing countries, because it is expensive and the health care infrastructure may not be adequate. More recently, findings from an NIH-supported trial in Uganda demonstrated that a single oral dose of nevirapine to the infected woman at the onset of labor, combined with a single dose of oral nevirapine to her infant within 72 hours of birth, reduced the risk of transmission by nearly 50 percent. This simplified, low-cost regimen has significant international implications. Nonetheless, more study is warranted concerning the safety of nevirapine for this use. In addition, it is critical to further identify cost-effective drug and nondrug approaches for preventing MCT. These include development of alternatives to breast-feeding, treatment of chorioamnionitis, and the use of caesarean section in some circumstances.

A safe and effective preventive vaccine is essential for the global control of the AIDS pandemic. The President has made discovery of an AIDS vaccine a national research priority. Consistent with this challenge, NIH has moved forward aggressively to build a comprehensive vaccine research enterprise. In recognition of the need to develop vaccines that are efficacious against a variety of strains found around the world, it is critical that NIH enhance international research efforts to analyze the genetic and antigenic variations of HIV and to target efforts toward eliciting cross-reactive immune responses. It will also be necessary to address the behavioral issues that pertain to conducting vaccine trials and those that pertain to the various groups' willingness to be vaccinated, once a product is available. Since such

issues will likely vary greatly from region to region and country to country, they will need to be addressed within the context of each individual country.

In the developed world, the advent of antiretroviral therapy has extended the length, and improved the quality, of life for many HIV-infected people. However, these drugs are expensive, difficult to administer and monitor, and entail significant challenges in patients' adherence. In the absence of antiretroviral therapy in much of the world, it is necessary to develop approaches to treat and prevent the opportunistic infections (OIs) that are the cause of morbidity and mortality, as well as to develop strategies for palliative care. As a foundation for development of such interventions, it is critical to characterize the nature, prevalence, and course of disease of the OIs found in diverse geographic settings and develop diagnostic methods to detect them. For mid-level income countries with a basic health care infrastructure, low-cost, alternative antiretroviral approaches may be feasible and should be investigated, including intermittent-treatment regimens and lower-cost antivirals and treatment combinations.

Recent studies of “therapeutic vaccines” that do not prevent infection, but can prevent or delay disease progression in animal models, offer opportunities for additional intervention strategies. The use of such a vaccine, in the context of at least some antiviral therapy, could potentially benefit humans, and it is a priority of the NIH vaccine program to pursue research in this area.

Globally, HIV/AIDS is the cause of much suffering—for those infected with HIV, for their families and friends, and for members of communities affected by AIDS. Research is needed to develop interventions to mitigate the negative consequences of HIV infection, particularly among AIDS orphans, including AIDS stigma.

The implementation of ethical considerations in international research, to the satisfaction of both the United States and the host country, can be a complex task, because of differences in areas such as law, regulation, and public policy; organizational structure; and cultural background. Research on ethical issues will help to identify how best to apply ethical principles in the design and conduct of intervention studies and in the implementation of results.

PRIORITY FOR FUTURE RESEARCH:

- **Conduct studies relevant to the geographic areas of the world and specific populations hardest hit by the epidemic.**

**TRANSLATION
OF RESEARCH
RESULTS**

To combat the raging pandemic, it is essential to implement the results of research that have an impact on the affected populations in developing countries. Further, ethical issues must be considered in planning for implementation of research results. Accomplishing these goals requires that research results be made available to policy makers in foreign governments, as well as to nongovernmental organizations and international organizations that develop programs to deliver health care, prevention, and other services. In addition, the research results must be interpreted in the context of the host country's social, cultural, economic, and political situation. To facilitate this process, the conduct of translational research is of critical importance, to better understand how to develop and implement programs in the relevant developing country context. Areas where translational research are urgently needed include strategies to reduce MCT, such as drug options and modification of breast-feeding practices, and the role of syndromic management of STDs.

To enable the widest possible dissemination of information to scientists and service providers, it will be necessary to improve access to such information through enhanced information technology. NIH's electronic information services currently are available through the Internet, and literature databases reflect the world's literature. Currently NIH is working to upgrade electronic communications in Africa.

The role of the mass media also needs to be considered, in creating an environment in host countries conducive to the conduct of research, and in assisting foreign governments and in-country organizations to implement the HIV-related programs that devolve from research. For example, the media can (1) inform the public about the role research plays in addressing the country's epidemic, (2) have a role in helping recruit study populations for studies such as trials of vaccines and other interventions, and (3) help inform target groups and the public about intervention programs such as condom campaigns, school-based educational programs, and MCT programs. Promoting this role for the media will require sustained efforts to educate the press, with ethical considerations chief among the issues to be addressed.

PRIORITY FOR FUTURE RESEARCH:

- **Enhance the translation of research results into action that will improve patient management, develop prevention programs appropriate to the setting, and effect policy changes.**

TRAINING OF FOREIGN SCIENTISTS

A cadre of trained investigators is a critical component of the infrastructure needed for conducting research in developing countries. This training will facilitate international collaborative research, as well as increase the capability of foreign investigators, institutions, and governments to independently conduct research to address their epidemics and to translate research results into clinical and public health practice. Areas of focus for training include epidemiology, development and testing of a wide variety of behavioral and biomedical prevention strategies, vaccine development, and development of indigenous substances as therapeutics. To build this capacity, NIH funds the AIDS International Training and Research Program (AITRP), which provides research training for scientists, health care providers, and public health workers from developing countries. The objectives of AITRP are to (1) increase the capacity of developing countries to deal with the AIDS epidemic through research and (2) stimulate cooperation and sharing of research knowledge by scientists worldwide. The AITRP provides training through grants to U.S. institutions; U.S. investigators develop relationships with in-country investigators and institutions. This program continues to link with the international research programs of the Institutes so that training supports the NIH research effort. Additional international training is conducted as an integral part of ongoing research programs such as the Centers for AIDS Research (CFARs), other HIV centers, the Prevention Trials Network, and the Vaccine Trials Network.

Although much of the training has, in the past, consisted of training foreign scientists in the United States, it is increasingly recognized that highly trained investigators who have returned to their home countries can serve as a training resource for other scientists in their own countries and geographic regions. Such “south-to-south” training should be encouraged to further increase the numbers of scientists who conduct high-quality research. In addition to being cost-effective, similarities in language, geography, cultural backgrounds, social contexts, and political and economic situations help to ensure that the training is relevant to the country and region.

For international research to be of high quality, it must meet the highest ethical standards. In this regard, it is essential to provide training for foreign scientists and members of ethical review committees in ethical issues related to the conduct of research.

PRIORITY FOR FUTURE RESEARCH:

- **Continue to enhance training for research needs, clinical capability and for technology transfer, building bridges with programs providing services, where possible.**

SCIENTIFIC PRIORITIES AND RESEARCH APPROACHES

PRIORITY FOR FUTURE RESEARCH:

- **Establish centers of excellence in international settings that will provide an environment that promotes the development of true and equal partnerships between U.S. and foreign investigators. These centers will support basic research and long-term cohort studies, serve as loci for studies of efficacy of biomedical and behavioral prevention interventions (including Phase I, II, and III vaccine trials), function as training centers for investigators from throughout the region, and serve as bridges with programs that provide services.**

RESEARCH APPROACHES:

- Involve foreign scientists in all stages of the research, including conceptualization of the research question, study design, development of protocols, study implementation and collection of data, data analysis, publication and presentation of research results, and interaction with the media.
- Improve and sustain laboratory capacity; transfer sustainable technologies.
- Improve clinical capabilities.
- Enhance the capability of foreign institutions to conduct independent ethical and scientific review.
- Enlist the participation of local communities, nongovernmental organizations, and governments in the development of research protocols.
- Consider the need for study participants and their communities in host countries to have maximum possible access to any preventive or therapeutic products developed during the research.
- Enhance the critical mass of trained in-country investigators.

PRIORITY FOR FUTURE RESEARCH

- **Conduct studies relevant to the geographic areas of the world and specific populations hardest hit by the epidemic.**

RESEARCH APPROACHES:

- Characterize OIs prevalent in diverse geographic settings and develop diagnostic methods, prophylaxis, and clinical management approaches appropriate to each setting.
- Develop strategies to prevent blood-borne transmission in health care settings, including blood screening strategies and technologies, and the role (i.e., use/misuse) of transfusion and injections.
- Develop biomedical strategies to prevent heterosexual transmission of HIV, such as microbicides, barrier methods, and syndromic management of STDs, with particular emphasis on women.
- Identify the biological determinants of infectiousness and susceptibility.
- Further identify cost-effective drug and non-drug regimens for preventing MCT.
- Identify effective palliative care approaches.
- Investigate low-cost alternatives to highly active antiretroviral therapy (HAART) that are feasible in resource-poor settings, including intermittent-treatment regimens, lower-cost antivirals and combinations, and the use of a therapeutic vaccine.
- Conduct research in areas important for vaccine development, including molecular epidemiology and behavioral issues.
- Develop the best sustainable, behavioral, economic, and environmental interventions for selected populations at risk, including adolescents, IDUs, and heterosexual men.
- Develop interventions to mitigate the negative consequences of HIV infection, particularly among AIDS orphans, including AIDS stigma.
- Conduct research on ethical issues.

FOR FUTURE RESEARCH:

- **Enhance the translation of research results into action that will improve patient management, develop prevention programs appropriate to the setting, and effect policy changes.**

RESEARCH APPROACHES:

- Conduct translational research in areas such as syndromic management of STDs, implementation of nevirapine for MCT, and breast-feeding practices.
- Provide improved access to information through enhanced information technology.
- Expand the role of the mass media.
- Consider ethical issues in planning for the implementation of research results.

PRIORITY FOR FUTURE RESEARCH:

- **Continue to enhance training for research needs, clinical capability and for technology transfer, building bridges with programs providing services, where possible.**

RESEARCH APPROACHES:

- Develop in-country training partnerships.
- Encourage south-to-south training.
- Support training in ethical issues related to the conduct of research.