FISCAL YEAR 2009

NATIONAL INSTITUTES OF HEALTH

TRANS-NIH PLAN FOR HIV-RELATED RESEARCH

Office of AIDS Research
National Institutes of Health
U.S. Department of Health and Human Services

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Dedicated to the memory of

DR. STEPHEN E. STRAUS

Founding Director of the National Center for Complementary and Alternative Medicine, Senior Advisor to the NIH Director, and Senior Investigator in the Laboratory of Clinical Investigation at the National Institute of Allergy and Infectious Diseases

A courageous and compassionate physician, scientist, leader, and friend

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Foreword

I am pleased to present the *Fiscal Year 2009 Trans-NIH Plan for HIV-Related Research*. I am grateful for the contributions and collaboration of many individuals who worked with us to develop this Plan. I thank the Directors of the NIH Institutes and Centers and their staffs; researchers from academia and industry; representatives from both domestic and international foundations and nongovernmental organizations; community representatives; representatives of other governmental agencies; and members of the Office of AIDS Research Advisory Council for their participation in the development of and thoughtful contributions to this document.

The overarching structure of the AIDS research plan is based on the need for: a strong foundation of basic science; research to prevent and reduce HIV transmission, including microbicides, vaccines, and behavioral interventions; research to develop better therapies for those who are already infected; research related to specific populations, including research related to women and girls; research in international settings; research targeting the disproportionate impact of AIDS on racial and ethnic populations in the United States; and research support and information dissemination.

This year we also have defined two critical research priorities that transcend the entire AIDS research portfolio: (1) prevention of acquisition and transmission of HIV, and (2) prevention and treatment of HIV-associated comorbidities, comortalities, and coinfections. These priorities represent the areas of research that will be targeted for new or reallocated funding in the development of the NIH AIDS research budget.

The *Fiscal Year 2009 Trans-NIH Plan for HIV-Related Research* defines the scientific challenges that lie before us. It will assist OAR to enhance trans-NIH collaboration and ensure that research dollars are invested in the highest priority areas of scientific opportunity that will lead to new tools in the fight against AIDS.

Jack Whitescarver, Ph.D.
NIH Associate Director for AIDS Research and Director, Office of AIDS Research
October 2007

Legislative Mandate

The National Institutes of Health Revitalization Act of 1993 (Public Law 103-43) provided that the Director of the Office of AIDS Research (OAR) "shall plan, coordinate and evaluate research and other activities conducted or supported" by the NIH. The Director of OAR "shall act as the primary Federal official with responsibility for overseeing all AIDS research conducted or supported by the National Institutes of Health" and "shall establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health…; ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; ensure that the Plan establishes objectives regarding such activities…; and ensure that the Plan serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of specific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan." The law further provides that "the Director of the OAR shall ensure that the Plan provides for basic research; provides for applied research; provides for research that is supported and conducted by the agencies; provides for proposals developed pursuant to solicitations by the agencies and for proposals developed independently of such solicitations; and provides for behavioral research and social science research."

Overview

Overview

The long-term response to AIDS depends on progress in HIV research. All aspects are needed from understanding the basic biology of HIV, developing effective therapies to treat HIV-related disease, understanding the determinants of HIV transmission, and evaluating the effectiveness of a variety of approaches to preventing new infections, including biomedical approaches such as microbicides, pre-exposure prophylaxis, HIV vaccines, male circumcision, and condoms.

Joint United Nations Programme on HIV/AIDS (UNAIDS)[1]

THE GLOBAL HIV/AIDS PANDEMIC

Over 25 years since the recognition of AIDS and the identification of HIV as its causative agent, the HIV/AIDS pandemic has become a global scourge that affects people in every country worldwide. UNAIDS reports that in 2007, more than 33.2 million people were estimated to be living with HIV/AIDS; 2.5 million people were newly infected; and 2.1 million died of AIDS-related illnesses.[2] The majority of people infected with HIV live in developing countries.

Africa has been disproportionately affected, and sub-Saharan Africa remains the most affected region globally. In 2007, more than 65 percent of all people living with HIV resided in sub-Saharan Africa. Obiageli Katryn Ezekwesili, Vice President, Africa Region, The World Bank, recently wrote, "HIV/AIDS poses an unprecedented development and human challenge, especially in Africa. In many countries, the epidemic has cut life expectancy and robbed society of millions of people in their prime working years. It has dimmed the hope of living full and productive lives for unimaginable numbers of infants, children, and young adults."[3] The epidemic has expanded in other parts of the world as well. UNAIDS reports that between the years 2001 and 2007, the number of people living with HIV in Eastern Europe and Central Asia has more than doubled.[4]

Dr. Peter Piot, UNAIDS Executive Director, stated, "[I]t is clear that AIDS investments are yielding results. In some countries, changes in sexual behaviour are having a measurable impact on infection rates, while the roll-out of HIV treatment in low- and middle-income countries has put almost three million people on antiretroviral drugs. Indeed, some countries have already achieved universal

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1 Science and Research. UNAIDS. Available at *http://www.unaids.org/en/PolicyAndPractice/ScienceAndResearch/default.asp*. Accessed September 8, 2008.

2 Report on the Global AIDS Epidemic. UNAIDS. Available at *http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008*. Accessed September 8, 2008.

3 Ezekwesili, Obiageli Katryn. The World Bank's Commitment to HIV/AIDS in Africa: Our Agenda for Action, 2007-2011. Available at *http://siteresources.worldbank.org/INTAFRREGTOPHIVAIDS/Resources/WB_HIV-AIDS-AFA_2007-2011_Advance_Copy.pdf*. Accessed September 8, 2008.

4 2008 Report on the Global AIDS Epidemic. UNAIDS. Available at *http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/*. Accessed September 8, 2008.

access to treatment, and some to prevention of mother-to-child transmission of HIV. But this is still just the beginning. HIV prevention continues to lag a long way behind. For every one person who starts taking antiretroviral drugs, another three become infected."[5]

The HIV/AIDS pandemic will remain the most serious public health crisis of our time until better, more effective, and affordable prevention and treatment regimens are developed and universally available.

AIDS AROUND THE WORLD

In 2007:

- Approximately 33 million people worldwide were living with HIV/AIDS.
- An estimated 2.7 million people were newly infected with HIV, including 370,000 children under the age of 15 years.
- Approximately 2 million people died due to AIDS.
- Women accounted for half of all infections.

Source: UNAIDS/WHO[6]

THE EPIDEMIC IN THE UNITED STATES

HIV/AIDS remains an unrelenting public health crisis in the United States, disproportionately affecting racial and ethnic populations, men who have sex with men (MSM), women of color, and young adults. The Centers for Disease Control and Prevention (CDC) reports that in the United States, more than a million people are infected with HIV. CDC has released new statistics showing that the number of annual new infections was actually higher than previously estimated, and the incidence of new infections has not declined for more than a decade. Since the beginning of the AIDS epidemic, there have been more than 565,000 cumulative AIDS deaths.[7]

According to the new CDC statistics, gay and bisexual men of all races and ethnicities and African American men and women are the most affected groups in the United States. Fifty-three percent of all new infections in 2006 occurred in gay and bisexual men. In 2006, blacks accounted for 45 percent of all new infections, even though they comprise only 13 percent of the total U.S. population.[8] Moreover, the overall prevalence of HIV/AIDS was more than 7 times higher for blacks than for

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5 Piot, Peter. 2007 UNAIDS Annual Report. UNAIDS. Available at *http://data.unaids.org/pub/Report/2008/jc1535_annual_report07_en.pdf*. Accessed September 8, 2008.

6 Report on the Global AIDS Epidemic. UNAIDS. Available at *http://www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/*. Accessed September 8, 2008.

7 Centers for Disease Control and Prevention. Cases of HIV Infection and AIDS in the United States and Dependent Areas, 2006. Available at *http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2006report/default.htm*. Accessed September 9, 2008.

8 U.S. Census 2000. Available at *http://www.census.gov/main/www/cen2000.html*. Accessed September 23, 2008.

Caucasians. In Washington, D.C., African Americans make up 57 percent of the population, yet they account for more than 80 percent of HIV/AIDS cases in the city. One in 20 people in Washington, D.C., is living with HIV infection, and one in 50 has AIDS.[9] This staggering prevalence is similar to that of some nations in sub-Saharan Africa.

National Institutes of Health (NIH)-sponsored research established the foundation for and demonstrated the safety and efficacy of antiretroviral regimens that have extended the length and quality of life for many HIV-infected individuals who have access to and are able to adhere to the treatment regimens and tolerate their toxicities. These treatment regimens are associated with a number of side effects and long-term complications that may contribute to AIDS-associated morbidities and mortalities, including malignancies, cardiovascular disease, neurological disease, and autoimmune conditions. In addition to the side effects of HIV treatment, numerous coinfections are associated with or are exacerbated by immune deficiency, including tuberculosis (TB), hepatitis B, hepatitis C, and malaria. In the United States, the maturing HIV/AIDS epidemic has the potential to generate concentric mini-epidemics of liver disease, tuberculosis, cardiovascular disease, and other HIV-associated morbidities, foreshadowing an epidemic of greater complexity in the coming years.

AIDS IN THE UNITED STATES

In 2006:

- Approximately 1.1 million Americans were living with HIV, including 448,871 with AIDS.
- Approximately 56,300 people were HIV-infected.
- 37,852 people were diagnosed with AIDS.
- More than 14,000 people died of AIDS.

Source: CDC[10]

THE NIH AIDS RESEARCH PROGRAM

The NIH supports a comprehensive program of basic, clinical, and behavioral research on HIV infection and its associated coinfections, opportunistic infections, malignancies, and other complications. The NIH investment in HIV/AIDS research is the largest and most significant in the world. The complexity, magnitude, and global nature of the epidemic necessitate a multifaceted, multidisciplinary, global research program. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of almost every NIH Institute and Center (IC).

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[9] Fauci, Anthony S., Statement on National Black HIV/AIDS Awareness and Information Day, February 7, 2008. Available at *http://www.niaid.nih.gov/about/directors/news/baaid_08.htm*. Accessed September 9, 2008.

[10] Centers for Disease Control and Prevention. Cases of HIV Infection and AIDS in the United States and Dependent Areas, 2006. Available at *http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2006report/default.htm*. Accessed September 9, 2008.

This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently. The NIH Office of AIDS Research (OAR), part of the Office of the NIH Director, was established in 1988 to coordinate the NIH AIDS research portfolio. Additional legislation, the NIH Revitalization Act of 1993, broadly expanded OAR's authorities to: coordinate the scientific, budgetary, and policy elements of the NIH AIDS program; prepare an annual comprehensive trans-NIH strategic plan and budget for all NIH-sponsored AIDS research; evaluate the AIDS research portfolio; identify and facilitate multi-Institute participation in priority areas of research; and facilitate NIH involvement in international AIDS research activities. To carry out its mandate, OAR has established unique comprehensive trans-NIH planning, budgeting, and portfolio assessment processes.

The Annual OAR Trans-NIH Planning and Budget Development Process

TRANS-NIH PLAN FOR HIV-RELATED RESEARCH

As mandated by law, the Director, OAR, develops the annual *Trans-NIH Plan for HIV-Related Research*. The Plan articulates the scientific priorities for AIDS research and is a roadmap for NIH investments in biomedical and behavioral AIDS research. It provides the framework to translate critical fundamental research findings, "from the bench to the bedside," both in the United States and abroad.

The *Trans-NIH Plan for HIV-Related Research* serves several important purposes. The Plan:

- Provides the framework for developing the trans-NIH AIDS research budget and monitoring those expenditures.
- Defines those research areas for which AIDS-designated funds may be allowed.
- Communicates the NIH AIDS research agenda to Congress, the scientific community, AIDS-affected communities, and the public. The *Trans-NIH Plan for HIV-Related Research* is available on the OAR Web site at *http://www.oar.nih.gov/strategicplan/*.

STRUCTURE OF THE PLAN

The Plan is organized into five functional chapters comprising Areas of Emphasis: (1) Foundational Research (Natural History and Epidemiology; Etiology and Pathogenesis); (2) Prevention Research (Microbicides; Vaccines; Behavioral and Social Science); (3) Therapeutics Research; (4) Research Support and Dissemination (Training, Infrastructure, and Capacity Building; Information Dissemination); and (5) Research Related to Specific Populations (Women and Girls; Racial and Ethnic Populations; Research in International Settings). Each Area of Emphasis of the Plan includes a comprehensive series of research Objectives, in priority order, that address the many needs and challenges within the field of HIV/AIDS research. Each Objective is followed by a list of Strategies that provide examples of approaches that may be taken to meet each Objective. All NIH expenditures of AIDS-designated funds are coded and tracked to the research Objectives in the Plan.

PLAN DEVELOPMENT

OAR has established a unique and effective multistep annual planning process that culminates in the development of the annual *Trans-NIH Plan for HIV-Related Research*. Through this process, scientific priorities for HIV-related research are identified for each of the Areas of Emphasis of the Plan. OAR initiates the annual planning process by convening a trans-NIH Coordinating Committee for each Area of Emphasis of the Plan. These Committees are chaired by the OAR senior staff

member responsible for each Area and include representatives of the ICs with major research portfolios in the corresponding Area. The Coordinating Committees develop a draft Plan by reviewing and updating the previous year's Plan, considering the state of the science, recent research results, and public health need. Each Committee revises the scientific Objectives and research Strategies for its Area of Emphasis as necessary. Each Committee also identifies the scientific research priorities within its Area of Emphasis.

Once the draft Plan is developed by the Committees, OAR seeks input from non-NIH scientists from academia, industry, foundations, other Government agencies, and community representatives by convening a Planning Group for each Area of Emphasis, except for the areas of Information Dissemination and Training, Infrastructure, and Capacity Building. Each Planning Group is asked to provide input on these two Areas as they relate to its specific Area of Emphasis.[11] The Planning Groups bring together non-Government experts with the NIH members of the Coordinating Committees to work together to further refine their sections of the Plan.

After the Planning Groups have met and refined the draft Plan, it is reviewed by the OAR Director and OAR senior staff, and overarching priorities are identified. The Plan then is provided to each IC Director and designated IC AIDS Coordinator for additional review and comment from the IC perspective, and finally to the OAR Advisory Council (OARAC) for its final review. The comments and suggestions of the participants at each stage of the Plan's development are considered in the development of the final document.

TRANS-NIH AIDS RESEARCH PORTFOLIO ANALYSIS

In fiscal year (FY) 2006, a multitiered, comprehensive trans-NIH review of all grants and contracts supported with AIDS-designated funds was added to the annual planning process. This review ensures that the AIDS research budget is used to support the highest priority science, taking into account the ever-changing domestic and international AIDS epidemic, as well as the evolving scientific priorities. This has become an integral component of the annual strategic planning and budget development process.

Each OAR staff member who chairs a scientific Coordinating Committee initiates a review of all NIH extramural projects that correspond to the Area of Emphasis of his or her Committee, concentrating on those projects eligible for recompetition in the fiscal year of the strategic Plan. Working with relevant IC program staff, OAR staff members identify projects that are no longer aligned with current top research priorities, which may have shifted since the projects were initially funded due to the changing demographics of the epidemic, scientific advances, and new opportunities. The determination of "lower priority for AIDS funding" is not related to the scientific or technical merit of the projects, only to their relevance within the current AIDS research priorities.

[11] A list of all of the members of the Planning Groups can be found at the end of this document.

After review of the grant portfolio by NIH and IC program staff, a group of eminent non-Governmental scientists reviews each scientific Area and all of the projects identified as lower priority and provides recommendations for redirecting funds to catalyze future initiatives and multidisciplinary endeavors. Next, OAR notifies each IC of those grants identified as too low a priority for support with AIDS dollars. The IC may choose to fund the project with non-AIDS dollars if the investigator chooses to submit a renewal application that is determined to be scientifically meritorious in the peer review process.

TRANS-NIH COMPREHENSIVE AIDS RESEARCH BUDGET

The *Trans-NIH Plan for HIV-Related Research* provides the framework for the annual budget development and allocation process. The ICs use the Priorities and Objectives articulated in the Plan to guide the formulation of their AIDS-related research budget requests to OAR, focusing on new or expanded program initiatives aligned with the current research priorities. OAR reviews the IC initiatives in relation to the Plan, the OAR priorities, and other IC submissions to eliminate redundancy and/or to ensure cross-Institute collaboration. The NIH Director and the OAR Director together determine the amount within the overall NIH budget to allocate for AIDS research. Within that total, OAR determines the AIDS research budget allocation for each IC based on the scientific priority of each proposed initiative. This process continues at each step of the budget development process up to the time of the final congressional appropriation. The careful determination of the balance of the research budget—among Institutes, among areas of science, between AIDS and non-AIDS research, between intramural and extramural research programs, between basic and clinical research, and between investigator-initiated and targeted research—requires a comprehensive knowledge of the science and of the Institute portfolios. Dollars are allocated to ICs based not on a formula, but on the priorities of the Plan, scientific opportunities, and the capacity of individual ICs to invest resources in the most meritorious science. At the time of the appropriation, OAR informs each IC of its AIDS-related budget allocation level, specifying amounts for each approved initiative. As each IC awards AIDS-related research grants, they are required to code those dollars to the appropriate Objective(s) of the Plan and report them to OAR.

DESCRIPTIONS OF THE AREAS OF EMPHASIS

CHAPTER 1, FOUNDATIONAL RESEARCH: Foundational Research addresses the basic science and building blocks upon which the rest of the research agenda is based. It encompasses the Natural History and Epidemiology and Etiology and Pathogenesis Areas of Emphasis.

- **Natural History and Epidemiology:** Natural history and epidemiologic research is essential for monitoring epidemic trends; following the changing clinical manifestations of HIV disease and associated coinfections, comorbidities, and comortalities in different populations; and measuring the effects of prevention strategies and treatment regimens. NIH-supported natural history and epidemiologic research has played a key role in elucidating the interplay of virus,

host, and environment. The changing face of the epidemic, with new groups and populations affected, necessitates the conduct of rigorous epidemiologic studies in different settings, both domestically and internationally. The NIH also supports the development of improved methodologies for studying the natural history and epidemiology of the HIV pandemic.

- **Etiology and Pathogenesis:** Etiology and pathogenesis research is focused on gaining a better understanding in two areas: (1) how HIV infection is established and maintained; and (2) what causes the profound immune deficiency and severe clinical complications that accompany HIV infection. Results of this research are the basic building blocks for the development of new drugs, vaccines, microbicides, and prevention strategies. Until HIV acquisition and transmission can be prevented and therapeutic regimens that cure HIV infection developed, support for basic etiology and pathogenesis research will remain a critical element in the fight against HIV/AIDS.

CHAPTER 2, PREVENTION RESEARCH: The Prevention Research chapter describes basic, clinical, and translational research on microbicide and vaccine development and behavioral and social science research associated with HIV transmission, acquisition, and care. There is an urgent need to expand the range of interventions for preventing HIV acquisition and transmission beyond those currently available. It is important to note that the NIH also supports research on a broad range of other prevention strategies, including studies on circumcision, prevention of mother-to-child transmission, and pre- and postexposure prophylaxis; however, these strategies are included within other scientific sections of this Plan. The magnitude of the global AIDS pandemic necessitates the simultaneous pursuit of multiple avenues of prevention research.

- **Microbicides:** Microbicides traditionally have been antimicrobial products that can be applied topically to the genital or gastrointestinal tract to prevent the acquisition of HIV and other sexually transmitted infections (STIs). More recently, antiretroviral agents and naturally occurring biologic agents, such as lactobacillus, are being studied in oral and topical formulations as ways to prevent HIV acquisition. Microbicides may offer one of the most promising primary prevention interventions that can be used alone or in combination with other prevention strategies to prevent acquisition and transmission of the virus. The NIH supports a comprehensive microbicide research program that includes the discovery, development, and testing of compounds with the potential to act as agents that prevent transmission and acquisition of HIV and other STIs. In addition, the NIH supports basic and clinical biomedical research that will assist in the understanding, development, and study of microbicides for use by both males and females. The NIH also supports the behavioral and social science research necessary to understand the issues of microbicides acceptability, adherence, and appropriate use in varied populations.

- **Vaccines:** The best long-term hope for controlling the AIDS pandemic is the development of a safe and efficacious HIV vaccine. The NIH supports a broad program encompassing basic, preclinical, and clinical research on vaccine candidates. The NIH also supports research to identify and better understand the complexities of protective immune responses, including the development

of improved animal models to conduct preclinical evaluation of vaccine candidates. Findings from these studies inform the design, development, and testing of novel vaccine strategies.

- **Behavioral and Social Science:** The NIH supports research to better understand how to influence the behaviors that lead to HIV transmission, including research on how to prevent initiation of such behaviors, and how to maintain protective behaviors once they have been adopted. The NIH sponsors research related to: developing, implementing, and evaluating behavioral and social science interventions which reduce HIV transmission in various populations and settings; strengthening our understanding of the determinants, trends, and processes of HIV-related risk behaviors and the consequences of HIV infection; and improving the methodologies employed in behavioral and social science research relevant to HIV prevention and treatment. Many of these methodologies are applicable simultaneously at several levels, including prevention of infection, provision of HIV care, and amelioration of the negative physical, psychological, and social consequences of HIV infection. A better understanding of social and cultural factors associated with HIV risk and/or protection, particularly in racial and ethnic populations, will contribute to the successful implementation of a broader range of preventive and/or therapeutic strategies.

CHAPTER 3, THERAPEUTICS RESEARCH: NIH-sponsored research identified the first targets for drug development using structural biology; developed the first drugs to treat HIV infection; and demonstrated the safety and efficacy of monotherapy, two-drug combinations, and multidrug antiretroviral therapy (ART) regimens to treat HIV disease. Groundbreaking NIH-sponsored studies demonstrated that the use of antiretrovirals dramatically decreases mother-to-child transmission of HIV. The NIH supports a comprehensive AIDS therapeutics research portfolio that includes discovery, preclinical development, and clinical testing of new drugs and multidrug therapeutic regimens, as well as studies of pre- and postexposure ART to prevent HIV infection. The NIH also supports the development of improved therapeutic strategies that may by utilized in resource-limited settings. Another critical area of therapeutics research supported by the NIH is aimed at combating HIV-related coinfections and comorbidities, such as tuberculosis, hepatitis C, malaria, malignancies, metabolic disorders, cardiovascular disease, and neurologic disorders.

CHAPTER 4, RESEARCH SUPPORT AND DISSEMINATION: The conduct of all phases of AIDS-related research requires trained scientists, clinical staff, and critical infrastructure, both domestically and internationally. The NIH provides support for these crosscutting areas, as well as for the dissemination of information to all constituent communities.

- **Training, Infrastructure, and Capacity Building:** The NIH supports the training of biomedical and behavioral AIDS researchers in the United States and internationally. The NIH also supports the infrastructure required for the conduct of AIDS-related research and clinical

studies in many locations, including resource-limited settings. Moreover, the NIH supports programs specifically designed to recruit individuals from underrepresented populations for research careers and to build research infrastructure at minority-serving institutions.

- **Information Dissemination:** Effective information dissemination approaches are integral to HIV prevention and treatment efforts. Such programs are critical in light of the continuing advent of new and complex antiretroviral treatment regimens, the adherence issues related to HIV/AIDS treatment, the need for research communities to work and communicate globally, and the need to translate behavioral and social prevention approaches into practice. The changing pandemic and the increasing number of HIV infections in specific population groups, such as racial and ethnic populations, MSM, and women, also underscore the need to disseminate HIV research findings and other related information to communities at risk. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to rapidly translate research results into practice and to shape future research directions.

CHAPTER 5, RESEARCH RELATED TO SPECIFIC POPULATIONS: Certain populations, including racial and ethnic populations and women and girls, are disproportionately affected by the AIDS pandemic. The NIH AIDS research portfolio includes research aimed at addressing the unique needs of these populations. (Funding for the Areas in this final Chapter is not tracked by Objective.)

- **Women and Girls:** The NIH supports studies of the mechanisms through which sex and gender confer vulnerability to, or protection from, HIV infection and AIDS among women and girls, in general and relative to men, in diverse geographical settings and during different stages of the life course. There are many research questions that remain unanswered about specific anatomical and physiological characteristics of women and girls that may play a role in transmission, acquisition, and/or resistance to HIV infection. The NIH supports studies that focus on factors in HIV acquisition, including the influence of hormonal modulation on viral replication, immune responses in the reproductive tract, and cofactors, such as coincident infections with other STI pathogens.

- **Racial and Ethnic Populations:** In the United States, HIV disproportionately affects racial and ethnic populations. The NIH supports research that may lead to the development of interventions that will impact these groups, including interventions that address the co-occurrence of other STIs, hepatitis, drug abuse, and mental illness, and interventions that consider the role of distinct cultural, family, and other social factors in the transmission and prevention of these disorders. The NIH is making a significant investment to improve research infrastructure and training opportunities for minorities and will continue to ensure the participation of racial and ethnic populations in AIDS clinical studies.

- **Research in International Settings:** For more than 25 years, the NIH has supported research efforts in countries affected by HIV/AIDS. The NIH has expanded its research activities to

encompass studies involving researchers in approximately 90 countries around the world through both intramural and extramural mechanisms. Results of this research benefit not only the people in countries where the research is conducted, but also people affected by HIV/AIDS worldwide. NIH-sponsored international research includes efforts to test products such as HIV vaccine and microbicide candidates; behavioral strategies targeted to the individual, family, and community to alter risk behaviors associated with sexual activity and drug and alcohol use; drug and nondrug strategies to prevent mother-to-child transmission; therapeutics for HIV-related coinfections and other conditions; and approaches to using antiretroviral therapy in resource-poor settings. Most of these funds are awarded to scientists in U.S.-based research institutions to conduct research in collaboration with scientists in the host countries. Some funds are awarded directly to investigators at research institutions outside of the United States.

Critical AIDS Research Priorities

During the development of this Plan, the Planning Groups for each Area of Emphasis were asked to identify the most critical research priorities in their Area. All of the suggested priorities were then considered by the OAR senior scientific staff. In the distillation of all the suggested priorities, two clear overarching priorities emerged to focus research across all of the Areas: (1) prevention of acquisition and transmission of HIV and (2) prevention and treatment of HIV-associated comorbidities, comortalities, and coinfections.

In addition, several specific priorities that transcended all Areas of Emphasis of the Plan were identified, including the application of genetics, genomics, proteomics, systems biology, and other related technologies to the study of HIV/AIDS and the host immune response; the interrelatedness of HIV/AIDS and nutrition; and the development and testing of research models, methods, and measures to accurately assess risk and protective behaviors in diverse populations. All of these priorities are essential to address the epidemic both in the United States and in international settings.

The overarching priorities are defined more specifically below. They will guide the development of the FY 2010 trans-NIH AIDS research budget and be utilized to adjust the FY 2009 AIDS budget as necessary.

Prevention of Acquisition and Transmission of HIV

The NIH will give highest priority to research that will:

- Advance understanding of the etiology and pathogenesis of HIV, including:
  - The host response to HIV and the overall capacity and complexity of the human immune system.
  - Genetic and biological mechanisms that govern the entry of HIV into target cells, particularly in relation to the interactions of HIV envelope, cell receptors, and mucosal surfaces.
  - Biological-behavioral interactions and social dynamics related to changes in transmission risks over the course of HIV infection and disease, such as those differentially associated with acute infection, recent diagnosis, chronic infection accompanied by antiretroviral treatment, and later-stage disease.
- Identify biomarkers and bioassays of HIV-host interaction at various stages throughout the entire course of HIV disease that are predictive of the efficacy and safety of biomedical interventions, including vaccines and microbicides.

- Develop and validate animal models that can be used in the preclinical evaluation of biomedical strategies for preventing the acquisition and/or transmission of HIV.
- Apply knowledge from basic research on HIV pathogenesis to the development of behavioral strategies and social interventions that prevent the establishment and spread of HIV between individuals and within communities.
  - Develop and evaluate novel biomedical strategies, including vaccines and microbicides, along with existing strategies, in clinical trial settings to inform and optimize future product design and application.
  - Develop and test methods of intervening at structural, environmental, and community levels to reduce acquisition and transmission of HIV. Focus attention on prevention strategies that can be implemented in racial and ethnic communities and in populations with a high incidence of HIV infection, such as MSM.

Prevention of HIV infection is the NIH's highest priority for AIDS-related research. There is an urgent need to expand the range of interventions for preventing HIV transmission beyond those currently available. The NIH AIDS prevention research portfolio includes basic, clinical, and translational studies on all aspects of biomedical and behavioral and social sciences research. This research may lead to the development of improved strategies for the prevention of HIV infection.

The disappointing results from recent clinical studies of HIV vaccine and microbicide candidates underscore the need for additional discovery (basic) research on HIV and the host immune response. Although NIH-funded AIDS research has yielded an impressive foundation of knowledge about the host response to HIV, the results from the recent trials indicate that a better understanding of the natural history, epidemiology, etiology, and pathogenesis of all phases of HIV infection and the host immune response is needed to enable the development of novel products that prevent the acquisition and/or transmission of HIV.

There is increasing recognition that biology and behavior interact in complex ways to affect HIV transmission and acquisition. For example, it is now clear that the probability of transmitting HIV very early in infection is higher than later in infection when viral load is lower due to ART, even given the same risk behaviors at both time points. Less clear are the complex interactions of behavioral and cellular events and the potential differential of susceptibility between individuals of different racial and ethnic backgrounds. The use of alcohol or drugs of abuse also may have both behavioral and health consequences that relate to susceptibility to infection.

Behavioral research studies have demonstrated that a number of existing interventions can have an impact upon HIV risk in targeted populations. The intensity of effort required to implement these interventions, as well as concerns about the sustainability of modified behavior, are concerns vis-à-vis large-scale implementation. There is a pressing need for research to determine the best means to scale up implementation and to determine where and when to best utilize existing strategies.

HIV transmission and acquisition also must be considered at the community level and within specific populations (e.g., MSM, racial and ethnic populations, women, etc.). There is a continuing need to better understand how HIV is transmitted in the course of human relationships that occur in social contexts that vary by location and culture. Interventions to reach and change the behaviors of large numbers of at-risk individuals are urgently needed, particularly interventions that target MSM, as well as men and women from racial and ethnic populations.

Prevention and Treatment of HIV-associated Comorbidities, Comortalities, and Coinfections

The NIH will give highest priority to research that will:

- Develop and evaluate new agents and drug regimens to prevent and treat comorbidities and comortalities (malignancies, cardiovascular diseases, metabolic disorders, and other complications) associated with long-term HIV disease and antiretroviral treatment.
- Develop and evaluate new strategies to prevent and treat HIV coinfections, including multi-drug-resistant (MDR) and extensively drug-resistant (XDR) TB, hepatitis C virus (HCV), and malaria.
- Identify genetic determinants of disease progression and treatment response and develop methods to optimize therapeutic regimens based on an individual's genomic sequence.
- Identify and evaluate the viral and host factors associated with ART failure.

The development of combination therapies for the treatment of HIV disease has resulted in extended survival and improved quality of life for those individuals who have access to antiretroviral drugs, can adhere to complicated treatment regimens, and can tolerate their toxicities and side effects. However, recent epidemiologic studies and clinical reports have shown an increasing number of malignancies, as well as cardiovascular and metabolic complications, associated with long-term HIV disease and ART.

Basic research is needed to better understand the pathogenesis of HIV disease, and the mechanisms of toxicity of antiretroviral drugs that contribute to the development of HIV-associated comorbidities and comortalities. Epidemiologic studies are needed to determine the incidence and prevalence of those associated with long-term HIV disease and ART in various populations, as well as to determine, monitor, and evaluate the effects of sex, gender, race, age, pregnancy status, nutritional status, and other factors on these ART complications. Clinical protocols that integrate studies on metabolic, endocrine, cardiovascular, neurologic, renal, and bone parameters are essential to better define these potential complications of ART and to develop regimens to prevent and treat these comorbidities.

Additional research is needed to define the mechanisms responsible for treatment failure and the development of strategies to maintain long-term undetectable viral load in HIV-infected individuals in the United States and internationally. This includes expanding research programs on drug resistance, drug toxicities, pharmacogenomics, nutrition, and adherence. Findings from these studies may benefit the development of improved strategies to prevent HIV transmission.

Recent advances in genomics have made it possible to identify genetic determinants associated with HIV disease progression and treatment response. Pharmacogenomics studies are needed to examine the inherited variations in genes that dictate an individual's response to antiretroviral therapies. In addition, studies are needed to explore how genetic variations can be used to predict the efficacy of and tolerability of antiretroviral medications in individual patients. Such studies might allow the development of future therapeutic regimens that can be custom formulated for an individual patient based on his or her genetic sequence.

The development of optimal strategies for the prevention and treatment of HIV coinfections (including TB, HCV, and malaria) requires additional basic and clinical research on the effects of these coinfections on HIV transmission, pathogenesis, and disease progression. Similarly, further studies are needed to determine the effects of HIV disease across the spectrum of its clinical course on the pathogenesis and progression of these coinfections. Additional pharmacokinetic and pharmacodynamic studies are critical to the evaluation of drug-drug interactions between antiretrovirals and agents used to prevent and treat coinfections associated with HIV.

CHAPTER 1

Foundational Research

Natural History and Epidemiology
Etiology and Pathogenesis

Natural History and Epidemiology

AREA OF EMPHASIS

Natural History and Epidemiology

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Transmission of HIV (Prevention, Risk Factors, and Mechanisms)*

Characterize the risk factors and mechanisms of HIV transmission in domestic and international populations to guide prevention and treatment strategies.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES

- Utilize existing cohorts, serodiscordant couples, and novel methods (e.g., social network analysis, molecular epidemiology, and geographic information systems) to further assess HIV transmission and acquisition.
- Model how results from existing cohorts might be altered in populations with differing demographics and socioeconomic status, specifically based upon race, ethnicity, gender, age, sexual orientation, acquisition risk, and in-country resource capacities and availability.
- Conduct molecular epidemiology studies to characterize the impact of different HIV types (i.e., HIV-1 and HIV-2), HIV subtypes, recombinant forms, and associated risk factors on routes and modes of HIV transmission, superinfection, natural history, response to antiretroviral therapy (ART) and preexposure prophylaxis (PrEP), and emergence of antiretroviral (ARV)-resistant viruses. Conduct studies that will determine the significance of multiple circulating subtypes and generation of dual, multiple, and recombinant viruses on population epidemiologic dynamics and potential implications for intervention and therapy.
- Conduct epidemiological and modeling research to improve estimates of per-contact risk of HIV transmission, based on type of sexual exposure, characteristics of the infected and uninfected partners (e.g., plasma and/or anogenital tract viral load, host genetics, and coinfections), and cofactors such as drug use.

Strategies Related to Transmission

- Evaluate sexual and blood-borne HIV transmission and acquisition in relation to the following:
  - Viral factors such as viral quantity, diversity, coreceptor usage, genotype (including subtypes, recombinants, and resistance mutants), and dual virus infections in various body compart-

ments (e.g., blood, saliva, semen, and mucosal compartments, such as the female genital tract and the anorectal mucosa);

- Host genetics and other host factors such as age, sex, race, hormonal status, comorbid chronic diseases, strength and breadth of immune response, circumcision status, mental health, and coinfections;
- Modifiable host factors such as diet and nutritional status, or drug, alcohol, and tobacco use and/or treatment, including substitution and other substance use treatment modalities;
- Other infections and their treatment, including *M. tuberculosis* (TB) and drug-resistant strains, multi-drug-resistant (MDR) and extensively drug-resistant (XDR) TB, *Plasmodium* sp. (malaria), and viral hepatitis;
- Social, cultural, and structural determinants of susceptibility to HIV acquisition (i.e., among women and girls and other adversely affected populations); and
- Sexual activity, abstinence (including during the postoperative period after male circumcision), sexual networks, choice of partner, multiple concurrent partners, duration of partnership, partner fidelity, control of sexually transmitted infections (STIs), hygienic practices such as douching, contraception choices, and cultural practices such as the use of traditional vaginal preparations and male circumcision.

- Further refine the timing, mechanisms, and risk factors in perinatal and postnatal transmission, including treatment of the mother, infant feeding modalities, physiology of lactation, long-term effects of perinatal interventions, maternal and infant genetic variation, and kinetics of viral resistance. These studies include:
  - Assessing the impact of maternal and infant ARV regimens of different potency and duration on mother-to-child transmission (MTCT) of HIV and on the short- and long-term health of women and their infants, and the emergence of ARV drug resistance in the mother and in those infants who become infected despite prophylaxis;
  - Studying the safety and effectiveness of sustainable approaches to prevention of MTCT of HIV, including identifying successful breastfeeding weaning strategies, methods for improving the safety of formula feeding, and determining the effects of such approaches on infant morbidity and mortality;
  - Assessing the impact of maternal ART on HIV transmission during pregnancy and lactation;
  - Assessing the impact of maternal and infant adherence to ARV regimens on the risk of subsequent ARV resistance, clinical outcomes, and the effectiveness of ART in mothers and their children;

- Assessing the impact of perinatal treatment and prophylaxis regimens on communitywide HIV resistance to ARVs;
- Assessing the impact of MTCT programs on public health measures, including maternal, paternal, and infant morbidity/mortality rates; overall life expectancy; disability and/or quality-adjusted life years; and pediatric neurobehavioral development; and
- Assessing clinical outcomes, cost, and cost-effectiveness of different strategies for prevention of MTCT in the United States as well as in developing countries.

Strategies Related to Treatment and Interventions

- Conduct epidemiologic modeling studies on the aggregate impact of ART on HIV transmission, particularly in high-prevalence settings.
- Study the impact of widespread ART availability, adherence, and patterns of ART resistance on HIV prevalence, incidence, patterns of risk behaviors, and acquisition of resistant HIV strains.
- Conduct further studies on male circumcision as a prevention tool, including:
  - Assessing the impact of adult male circumcision on an individual and community level, including assessment of HIV prevention and incidence in circumcised males and their partners, sexual behavior, and attitudes, in the domestic and international setting;
  - Evaluating male circumcision delivery models with respect to safety, cost-effectiveness, and long-term impact on HIV transmission;
  - Evaluating male circumcision and its impact on HIV transmission and acquisition among men who have sex with men (MSM); and
  - Evaluating prevention approaches in the context of adult male circumcision, particularly those based on combinations of known methods, including reproductive health, partner reduction, condom use, and STI control.
- Develop and evaluate safe and effective individual-, network-, and community-based interventions aimed at HIV-infected persons and their partners to promote sustained behaviors that prevent acquisition and transmission of HIV.
- Conduct studies on medication-assisted substance abuse treatment modalities and access to care (e.g., methadone maintenance, buprenorphine/naloxone, naltrexone, antabuse, acamprosate, and stimulant abuse therapy), alone or in combination with mental health and/or behavioral interventions, as HIV prevention interventions.

OBJECTIVE–B: *Disease Progression (Including Opportunistic Infections)*

Use epidemiological research in domestic and international settings to identify the influence of therapeutics and other biological (e.g., age, host genetics, coinfections, HIV subtypes, and viral genetic variation) and behavioral (e.g., access to and use of the health care system, adherence, and alcohol and drug use) factors on HIV progression and response to therapy, as demonstrated by virologic, immunologic, and clinical outcomes.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES

Strategies Related to Disease Progression and Response to ART

- Investigate the effect on disease progression of viral factors, including viral type/subtype, fitness, viral tropism, and innate and acquired genotypic and phenotypic resistance to ARVs.
- Determine the global patterns of innate and acquired viral resistance to ART and how these patterns could influence the long-term effectiveness of these therapies.
- Elucidate the pathogenic mechanisms that influence residual HIV replication or reservoir latency in ART recipients, including tissue and lymphoid reservoirs, and body secretions such as cervicovaginal fluids and semen.
- Investigate the contribution of innate host characteristics to viral measures, immune function, disease progression, and mechanisms for these effects, including host genetic factors and their modulators, sex, race, and age.
- Examine how chronic inflammatory processes and mediators such as inflammatory cytokines modify immune function, disease outcomes and survival, and response to ART.
- Characterize the changing spectrum of clinical outcomes, causes of morbidity and mortality, and complications of therapy associated with evolving therapeutic strategies, domestically and internationally.
- Assess the effect of ART treatment on the incidence and pathogenesis of and risk factors for cancer in the domestic and international settings.
- Define the prevalence, incidence, predictors, potential treatments of, and consequences of renal and liver disease in HIV-infected individuals.
- Characterize the long-term effect of HIV infection on the central nervous system, including the effect of viral burden in the cerebrospinal fluid (CSF), its effect on white matter degeneration, and the role of ART in reducing the neurocognitive burden of disease and differentiating these changes from other neurocognitive diseases, such as dementia and Alzheimer's disease.

- Evaluate and characterize immune reconstitution, including modifiable and nonmodifiable predictors of immune recovery in diverse populations.
- Define the prevalence, incidence, and determinants of HIV-associated neurologic, behavioral, and psychiatric manifestations and their relation to disease progression and response to ART, domestically and internationally.
- Identify, characterize, and determine the frequency, changing manifestations, and effects of HIV-related respiratory disease on morbidity, mortality, and HIV disease progression, in both untreated patients and those receiving ART (e.g., recurrent bacterial pneumonia; drug-resistant, MDR-TB, and XDR-TB/HIV cases; immune reconstitution syndromes affecting the lungs, including sarcoidosis and other immune-mediated diseases; HIV-related pulmonary hypertension; accelerated emphysema; and coinfections).
- Develop new interval-based or standard-of-care cohorts and maintain long-term followup of existing cohorts, including observational cohorts and intervention populations, to determine the changing spectrum of HIV disease, identify highly exposed uninfected persons and long-term nonprogressors, and evaluate interventions, especially in aging and minority populations, in developing countries, and in emerging epidemic zones, including Central Asia, the former Soviet Union, and South and Southeast Asia.
- Characterize short- and long-term consequences of recent HIV infections including host and viral genetic characteristics and differences by route of exposure, and continue to characterize the natural history of HIV disease and AIDS among those early in infection, those with minimal exposure to ART, those with virologic and/or immunologic responses to ART, and those who have experienced ART failure.

Strategies Related to Complications of Therapy

- Comprehensively determine the effects of cumulative and current antiretroviral therapy exposure to specific drugs, classes of drugs, drug combinations, and treatment strategies.
- Characterize and investigate the role of ART-associated toxicities (including disorders in glucose, lipid, and bone metabolism, renal dysfunction, and hepatotoxicity) in specific populations, including coinfected populations (e.g., TB, XDR-TB, hepatitis C [HCV], and hepatitis B [HBV]), pregnant women, children and adolescents, the aged, populations receiving traditional medicines, resource-limited populations, minority populations, and according to nutritional status, in comparison with non-HIV-infected populations.
- Investigate age and gender differences in ART-associated toxicities and comorbidities in comparison with non-HIV-infected populations. Gender differences should also explore differences in sex steroid levels (androgens and estrogens) and ovarian reserve in women and how they impact metabolic, cardiovascular, bone, renal, and liver disorders.

- Investigate the role of chronic inflammation in the development of malignancies and metabolic, cardiovascular, bone, renal, and liver disorders in HIV-infected individuals and appropriate controls and how cumulative and current ART use might mediate the effects of chronic inflammation.

Strategies Related to Comorbidities

- Intensify research on the spectrum of HIV-associated malignancies, particularly those that may develop in HIV-infected patients who have responded to ART and are expected to live longer with immune deficiency.
- Establish normative data for lymphocyte subsets, total white blood cell count, and total lymphocyte count, and determine the influence of common comorbidities, such as malaria, TB, and helminthic infections, on the "normal" values in patients from different regions of the developing world affected by the HIV epidemic, notably in Africa and Asia.
- Investigate TB–HIV interactions, including the effects of dual infection on the infectiousness and progression of both TB and HIV, and the effect of various treatment strategies on disease control and TB drug-resistant strains.
  - Investigate the XDR-TB epidemic, evaluating risk factors for XDR-TB prevalence, incidence, and therapeutic options among HIV-infected patients.
  - Develop novel TB diagnostics for use with HIV-infected patients in order to rapidly identify MDR-TB and XDR-TB in HIV/TB-coinfected populations.
  - Assess outcomes related to methods of integrating TB and HIV care on survival, quality of care, and cost.
  - Investigate the impact of treating latent TB on the epidemiology of HIV/TB coinfection in endemic countries to determine whether it is feasible, effective, and cost-effective.
- Evaluate the impact of treatment of alcohol use and abuse, illicit drug use, and mental health disorders on the effectiveness and consequences of ART, HIV disease progression, morbidity, and mortality.
- Support research efforts to link existing databases on cancer, TB, transplant, etc., and death registries to enhance understanding of HIV/AIDS outcomes in standard-of-care cohorts.
- Assess the interaction of HIV infection and ART on other infections and their treatment.
- Study the emergence and reemergence of infectious diseases and the development of antimicrobial-resistant infections (e.g., MDR-TB, sulfa-resistant malaria, antibiotic-resistant pneumococcus, cotrimoxazole-resistant *Pneumocystis jiroveci* pneumonia, methicillin-resistant *Staphylococcus aureus* [MRSA], and lamivudine-resistant HBV) in HIV-infected populations.

- Estimate the prevalence of specific human papillomavirus (HPV) types associated with cervical cancer and high-grade dysplasia in HIV-infected women, and evaluate the effectiveness of HPV vaccines among HIV-infected individuals from geographically diverse regions.
- Assess the interaction of ARVs on HPV persistence and regression of cervical lesions to understand the dynamics of the two viruses with a goal of optimizing care for HIV-infected women, especially in resource-limited settings.
- Assess the effect of primary care screening and interventions (e.g., statin use, hypertension management, smoking cessation, depression treatment, and cancer screening and treatment) on HIV disease outcomes and survival. Use these assessments to guide recommendations for adaptation and prioritization of primary care guidelines for those with HIV infection.

Strategies Related to MTCT and Pediatric Infection

- Study HIV-infected and -uninfected children and adolescents to determine factors related to impaired growth and neurodevelopment; cognitive, behavioral, and psychomotor development; impact of other childhood infectious diseases and nutritional status; and safety and efficacy of immunizations, and how these may be affected by biomedical and behavioral interventions.
- Study the effect of the health status of HIV-infected mothers and of ART during pregnancy, lactation, and early childlife on survival and quality of life of their HIV-infected and -uninfected children.
- Investigate the long-term outcome of complications due to HIV and ART use in HIV-infected pediatric populations as these children reach adolescence and adulthood.
- Assess the implications and outcomes of different strategies of prevention of MTCT on transmission and costs of care in HIV-infected mothers and their infants.
- Evaluate the differences in treatment response and HIV outcomes between adolescents, adults, and perinatally infected children; in behaviorally acquired versus perinatally infected adolescents; and in adolescents treated in pediatric versus adult HIV treatment centers.

Strategies Related to Aging

- Investigate the relationship between HIV infection and the spectrum of physical and mental health outcomes that increase with aging, such as cancer, obesity, diabetes, hypertension, arthritis, unexplained anemia, anemia of chronic inflammation, emphysema, renal insufficiency, and dyslipidemia, as they affect disease outcomes (e.g., liver disease, cardiovascular disease, and renal disease) and survival.
- Study the incidence and determinants of physical and cognitive decline in aging HIV-infected individuals, and the effect of frailty and functional impairment on HIV, ARV use, and self-care behaviors.

- Evaluate immunologic and virologic measures of HIV disease progression and mortality in older versus younger adults receiving ART to refine treatment guidelines for older HIV-infected patients, including the appropriate CD4 cell count for initiation of ART.
- Study the effects of HIV and ART, such as immunologic and virologic response to treatment, and adverse effects, in aging populations that have coexisting morbidities and who receive numerous medications.
- Develop guidelines to help prioritize treatment of comorbidities when managing HIV in older patients with multiple diseases.
- Study the impact of expanding routine, voluntary HIV testing in improving diagnosis, care, and outcomes in elderly patients.

Strategies Related to Adherence, Access to Care, and Quality of Life

- Develop and evaluate novel methods, such as behavioral reports and biological markers of use, for accurately measuring adherence to therapy and efficacy of preventive therapies in patients throughout the lifespan.
- Study determinants of adherence to ART and adverse events of ART in all age and risk groups, as well as in times of transition such as pregnancy and growth from child to adolescent to adult, to inform interventions to improve adherence.
- Study the impact of access to care, ART, microbicides, and vaccines on risk behaviors and HIV acquisition among at-risk populations, including minorities, MSM, and adolescents.
- Investigate how different patterns of access, adherence, and exposure to ART in treatment-experienced and -inexperienced populations contribute to ARV resistance and disease progression.
- Elucidate the effects of HIV infection on pain and sleep disturbances, including prevalence, possible immunological and endocrine mechanisms, associations with HIV outcomes, possible changes with ART, and influence on quality of life and physical and mental health.
- Develop studies on the impact of routine, voluntary HIV testing, and its role in different prevalence settings in improving HIV-related outcomes.
- Examine predictors of successful linkage to and retention of HIV-infected patients in care, from the time of HIV testing through the time of ART provision and patient followup.
- Assess the impact of different approaches for testing, linkage, and retention in care in improving overall outcomes of HIV disease.

OBJECTIVE–C: *Methodologies*

Develop and evaluate methods and resources for HIV/AIDS epidemiological and clinical studies that use culturally appropriate approaches; incorporate new laboratory, sampling, and statistical methods with information systems; and better integrate research findings into clinical practice and regional, national, and international policy.

(The scientific objectives of A, B, and C are of equal weight.)

STRATEGIES

- Evaluate and promote the use of multiple study designs that incorporate appropriate ethical, cultural, and policy context for studies of HIV disease and AIDS in diverse domestic and international populations.
- Continue to support local, regional, and international collaborations to integrate and harmonize existing data for scientific investigations.
- Ensure that the population composition of domestic epidemiological studies reflects the shifts in the populations at risk for and affected by HIV/AIDS, including older Americans, MSM, adversely affected racial and ethnic populations, and those with other comorbidities.
- Involve representatives of the community and study participants in all phases of research planning, design, management, approval, and reporting, when possible and appropriate, and promote and support academic/community-based research collaborations.
- Implement research training and career development opportunities for medical and health professionals from communities disproportionately affected by the epidemic, both in developing countries and domestically. Training should include research ethics, study design, informatics, biostatistics and modeling, data management and analysis, manuscript preparation and publication, grant writing, and translational research to promptly bring basic science results to clinical care and clinical results to health policy and implementation.
- Promote study designs that provide the highest degree of human subject protection and benefit possible.
- Promote study designs that include plans for dissemination of findings to community representatives, study participants, health care practitioners, and policymakers.

Strategies Related to Natural History/Pathogenesis

- Develop epidemiologic, laboratory-based, and simulation modeling methods in conjunction with prospective cohort studies, domestically and internationally, to monitor response to ART and the incidence of complications related to chronic use of ART, including:

- Develop and test methods to produce accurate, reproducible, and inexpensive virologic, immunologic, bacteriologic, pharmacologic, neurobehavioral, and genetic assays suitable for large-scale epidemiological research and surveillance in developing nations. Emphasis should be on simple and reliable staging of disease progression for the initiation and monitoring of ART and opportunistic infection (OI) prophylaxis; hepatitis testing; HIV resistance testing; and noninvasive, rapid, and inexpensive diagnostic assays for sexually transmitted diseases (STDs), other coinfections including malaria, TB and XDR-TB, and malignancies.
- Develop, maintain, and effectively cultivate ongoing and newly developed cohort studies, domestic or international specimen repositories, and databases for interdisciplinary HIV-related studies. Nested studies that utilize these resources should be particularly encouraged and developed.
- Use observational data to better characterize the natural and treated history of AIDS-associated conditions in international settings and trends in the epidemiology of these conditions.
- Identify and/or develop uniform assessment tools to measure host and environmental characteristics, including substance abuse and mental health, which may affect immediate and longer-term HIV-related health outcomes. Assessment tools should be both culturally appropriate and scientifically valid.
- Develop assays to identify recent HIV infection, including measures appropriate for international populations.

Strategies Related to Research on Design and Analysis of Epidemiologic Data

- Develop new epidemiological designs and statistical methods, including development of informatics tools and simulation, to better characterize transmission dynamics and monitor long-term trends in disease progression and development of toxicities in the setting of potent ART.
- Continue to develop and improve upon quantitative methods for making effective and appropriate use of data from large observational, cross-sectional, and cohort studies, such as:
  - Assessing costs of care for HIV disease management and treatment of comorbidities, both domestically and internationally;
  - Methods for inferring causal effects of nonrandomized exposures (e.g., treatment and policy changes);
  - Methods for estimating HIV infection rates in cross-sectional samples;
  - Methods for sampling hidden populations (e.g., respondent-driven sampling);
  - Models and inferential methods for characterizing multiple disease processes and events;

  - Methods for linking cohort data to cost data for direct health policy questions;
  - Methods for innovative study designs that can simultaneously address more than one hypothesis or intervention, including factorial randomized trials and quasi-experimental designs; and
  - Methods for collecting and analyzing spatio-temporal data, especially as they relate to transmission and spread of HIV infection.

- Encourage research on innovative design and analysis through interdisciplinary collaboration between methodologists from different fields, such as biostatistics, econometrics, epidemiology, computer science, biomathematics, decision sciences, operations research, health services research, and demography.

Strategies Related to Interventions

- Study and evaluate the various operational strategies that can be employed to "bring to scale" and to evaluate countrywide ART programs and successful preventive or therapeutic interventions, such as male circumcision, including the use of operations research and integrated observational databases to evaluate treatment effectiveness and cost-effectiveness at the individual, community, and population levels.
- Study and evaluate prevention packages that combine multiple strategies into one intervention, especially those that combine behavioral, biological, and structural interventions.
- Determine the outcome of different approaches to routine, voluntary HIV testing in different settings and in different racial/ethnic populations.
- Assess the optimal algorithms for HIV diagnosis in patients, including strategies for identification of acute infection.
- Assess the effectiveness and outcomes of clinical and/or laboratory monitoring for the initiation, monitoring, and switching of ART, particularly in resource-limited settings, including laboratory monitoring with new methods that are technologically appropriate and affordable in various international settings.
- Develop appropriate clinical and laboratory definitions of short- and longer-term ARV failure, and develop mechanisms for monitoring and assessing drug resistance evolution in HIV types, subtypes, and variants in domestic as well as international settings.
- Develop, evaluate, and promote new, improved, and cost-effective methods to prevent HIV transmission via blood transfusion, as well as other medical interventions and iatrogenic exposures in developing countries, including instrument sterilization.

- Assess the impact and cost-effectiveness of different strategies for HIV testing and linkage to and maintenance in care of different populations, including adolescents, seniors, racial and ethnic populations, and populations in diverse international settings.
- Develop strategies to validate the use of surrogate markers for HIV acquisition and/or transmission risk, including use of behavioral measures and biomedical markers.
- Develop and refine simulation strategies, such as modeling, to assess the impact of interventions on HIV transmission, cofactors of HIV infection, and communitywide morbidity and mortality, including non-HIV-infected individuals.

Strategies Related to Policy

- Develop studies of operational research and implementation science, which is the evaluation, translation, optimization, and scale-up of prevention, treatment, and health care innovations into effective new public health programs.
- Develop research efforts that measure and evaluate the outcomes of large-scale HIV treatment programs, with attention to clinical as well as economic outcomes of care.
- Evaluate the long-term clinical and nonclinical impact, cost, and health care utilization ramifications of different strategies for care, including treatment of HIV-associated conditions, ART, complications of ART, and other comorbidities.
- Assess the impact and acceptability of routine, voluntary HIV testing programs, including issues such as stigma and confidentiality.
- Support HIV policy research, including studies of laws and economics, necessary for translating epidemiological and clinical studies into policy to improve health and to make cost-effective decisions.
- Assess the impact of strategies for managing HIV coinfections in international settings using modeling and other integrative methodologies.

Etiology and Pathogenesis

AREA OF EMPHASIS

Etiology and Pathogenesis

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Biology of HIV Transmission*

Delineate the viral, host genetic, and immune mechanisms involved in the transmission, establishment, and spread of HIV infection in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives A and B are of equal weight.)

STRATEGIES

- Determine the role of phenotype/genotype/fitness and dose on transmission of cell-free and cell-associated HIV, in various bodily fluids at different portals of entry.
  - Define the role of cell-free and cell-associated HIV in various modes of transmission.
  - Determine the mechanisms by which virus-encoded genes and viral gene products regulate HIV infection and replication, and influence transmission, establishment, and spread of HIV infection.
  - Delineate the mechanisms by which host-encoded genes and gene products regulate HIV infection and replication, and influence the transmission, establishment, and spread of HIV infection.
  - Determine the role of the host microbiome in transmission, establishment, and spread of HIV infection.
  - Elucidate the genetic complexity and the biological characteristics of viruses that are transmitted during sexually acquired acute and early HIV infection.
  - Determine the structures of and interactions between viral and host proteins that are important for the transmission, establishment, and spread of HIV infection.
  - Determine the cell subsets and tissue types that serve as portals of entry and dissemination of HIV and that support replication during different stages of infection.
- Delineate the mechanisms by which innate and adaptive immunity, and the effects of genetic or environmental factors on innate and adaptive immunity, influence HIV replication and modulate transmission, establishment, and spread of HIV infection.

- Investigate the role of inflammation and its mediators in tissue on HIV transmission and dissemination.
- Delineate the mechanisms by which sexually transmitted infections (STIs) and coinfections influence HIV transmission, replication, establishment, and spread.
- Evaluate the influence of prevention and treatment on the early events in HIV transmission, establishment, and spread.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, epigenetics, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, and cellular biology) to understand the etiology and pathogenesis of HIV infection.
- Further develop, validate, and utilize experimental human, nonhuman, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of HIV/SIV (simian immunodeficiency virus) infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Define markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in human mucosal tissues. This would include humoral immunity and cell-mediated immunity at mucosal surfaces.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative as well as functional virologic and immunologic assays.
- Support and expand innovative research on the transmission, establishment, and spread of HIV infection.
- Develop and utilize natural and innovative technologies to procure, maintain, and expand the availability of nonhuman primate (NHP) models of both pathogenic and nonpathogenic infection and facilitate collaborative research using these models.

OBJECTIVE–B: *HIV Virology and Pathogenesis*

Delineate the viral and host mechanisms associated with the pathogenesis of immune dysfunction, aberrant immune activation/inflammation, and disease progression in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives A and B are of equal weight.)

STRATEGIES

- Define the factors that regulate initial HIV replication, control virus during primary infection, and establish viral setpoint.
- Determine how early events that regulate the establishment and systemic spread of HIV infection define the later clinical course of the disease in HIV-infected populations.
- Define the viral, host, pharmacologic, copathogenic, and environmental factors that contribute to disease progression and nonprogression.
- Define the virologic and host factors that enable HIV to establish and maintain a persistent infection *in vivo* in the setting of both drug-naive and drug-treated individuals.
- Delineate the mechanisms of host immune control of HIV replication and investigate how the effectiveness of immune control may vary through the course of infection, depending on the identity and location of infected host cells and the influence of therapeutic interventions.
- Delineate the molecular mechanisms by which virus-encoded genes, viral gene products, host cellular factors, and intracellular compartments regulate HIV replication and influence pathogenesis.
- Determine the factors that influence the susceptibility of target cells to HIV infection and their ability to support HIV replication.
- Determine the structures of complexes between viral proteins and host factors involved in the processes that underlie HIV disease progression.
- Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of immune cells and tissues in humans and NHP models, focusing on:
  - the loss of specific CD4+ T lymphocyte subpopulations and clones;
  - the impact of HIV infection on T-cell population numbers, specificities, and functions;
  - HIV-triggered immunopathogenesis, including immune activation, cell death, induction of nonresponsiveness, dysregulation in the number and function of immune effector cells other than T lymphocytes, and production of host factors, including cytokines and other mediators;

  - the structural and functional compromise of primary and secondary lymphoid organs (e.g., gastrointestinal mucosa) including hematopoietic precursor cells and their microenvironment;
  - influences on the developing immune system; and
  - disruption of host compensatory mechanisms that govern the generation, regeneration, and homeostasis of T-cell populations.
- Determine the contribution of immune activation/inflammation to HIV disease progression, and elucidate the mechanisms driving this activation.
- Determine the consequences of long-term physiological and/or immunological damage caused by HIV disease and/or HIV therapy.
- Evaluate whether and to what extent viral-induced damage to the systemic and mucosal immune systems can be reversed following suppression of HIV replication by therapeutic interventions.
- Determine the lifespan and developmental and regenerative pathways of T lymphocytes in humans and NHP models; elucidate the mechanisms that regulate the size and composition of T-cell populations and how these may change with antiviral treatment and with age.
- Define viral and host markers and functional assays that will enhance our understanding of and ability to study innate and adaptive immune function in humans, especially those approaches that permit study of the *in vivo* activity of the immune system.
- Define the reservoirs of virus in both acute and chronic infection that permit HIV persistence throughout the course of HIV infection, including in the setting of therapies and in the presence of ongoing immune responses.
- Determine the viral and host factors associated with clinical response and lack of response to therapeutic interventions in HIV-infected subjects.

To facilitate the research goals listed above:

- Further develop and utilize experimental human, nonhuman, *ex vivo*, and theoretical/math-ematical models to study the pathogenesis of lentiviral infections with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote augmented access to and sharing of key patient samples, animal model resources, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses

such as genomics, proteomics, and cellular biology) to understand the immunopathogenesis of HIV infection.

- Enable the translation of basic and preclinical research findings into clinical studies in humans to advance the understanding, treatment, and prevention of HIV infection.

OBJECTIVE–C: *Pathogenesis of Opportunistic Infections*

Elucidate the pathogenic mechanisms and consequences of opportunistic infections (OIs) and coinfections in HIV-infected individuals in diverse populations across the spectrum of age and gender in national and international settings and the factors that regulate susceptibility to OIs that might be targeted for prevention. Priority should be given to OIs and coinfections that (a) are a major cause of morbidity and/or HIV disease progression in HIV-infected individuals (e.g., tuberculosis [TB] and hepatitis C [HCV]) or (b) contribute significantly to HIV transmission or acquisition (e.g., sexually transmitted infections [STIs]).

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Conduct studies of the basic biology of such opportunistic pathogens and their interaction with the host.
- Identify and elucidate the genetic and environmental risk factors associated with the susceptibility to, the development of, and the progression of OIs in HIV-infected individuals.
- Study the effects of OIs and coinfections on immune dysfunction and HIV disease progression.
- Define immunologic responses to OI/coinfection pathogens at mucosal surfaces and determine how they may be altered by HIV infection.
- Study how HIV infection changes the pathogenesis of the coinfecting pathogens (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]).
- Elucidate the mechanisms of immune function that mediate protection against OIs.
- Study the effects of HIV therapy-associated immune reconstitution on the clinical course and manifestation of OIs and coinfections.
- Probe the pathogenic mechanisms of HIV-associated OIs, and evaluate how the causes, agents, and manifestations of these HIV-associated infections are altered by antiretroviral therapies (ARTs).
- Define the molecular and phylogenetic characteristics of major AIDS OIs and pathogens; standardize and improve techniques of phylogenetic analysis; and integrate strain-specific characterization of data into studies of the pathogenesis, mechanisms of transmission, and epidemiology of OIs.
- Determine the influence of the human microbiome on protection or susceptibility to OIs, coinfections, and HIV disease progression.

- Determine factors associated with clinical response and lack of response to therapeutic interventions against OIs and coinfections in HIV-infected subjects.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics and cellular biology) to understand the etiology and pathogenesis of HIV coinfections and HIV-related OIs.
- Develop *in vitro* techniques and animal models to propagate and define the life cycles of the opportunistic pathogens associated with HIV disease.
- Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated OIs, including stable, inexpensive, easy-to-perform assays appropriate for use in developing countries.
- Facilitate collaborative and interdisciplinary studies to elucidate the etiology and pathogenesis of HIV OIs and coinfections (e.g., TB and HCV).

OBJECTIVE–D: *Pathogenesis of Metabolic and Body Composition Change*

Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related metabolic disorders, body composition changes, endocrine dysfunction, and cardiovascular disease in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Define the mechanisms underlying alterations in metabolism, body composition, endocrine function, growth and development, and the risks of atherosclerotic cardiovascular, vascular, renal, bone, skeletal muscle, and skin disease to determine:
  - the effects of antiviral therapies and suppression of virus replication;
  - the influence of disease stages, including the degree of initial immunosuppression and immune reconstitution;
  - the contributions of individual virologic and host factors, including genetic loci; and
  - the contributions of OIs, hormonal dysregulation, and other consequences of HIV infection.
- Study the impact of HIV on an aging population, including the implications of HIV infection for cardiovascular, metabolic, bone, skeletal muscle, skin, and renal diseases.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms underlying alterations in metabolism, body composition, growth and development, diabetes, and bone, skeletal muscle, skin, renal, and atherosclerotic cardiovascular disease.
- Determine factors associated with clinical response or lack of response to therapeutic interventions against AIDS-associated metabolic and body composition changes, impaired growth and development, diabetes, and bone, skeletal muscle, skin, renal, and atherosclerotic cardiovascular disease.

To facilitate the research goals listed above:

- Transfer expertise from the endocrine, metabolic, cardiovascular, obesity, renal, bone, skeletal muscle, and skin research fields to the HIV field and promote linkage between HIV researchers and established individuals and centers of excellence in these areas of research. Encourage and facilitate collaborative and interdisciplinary research in these areas.
- Promote programs to facilitate access to and sharing of patient samples, animal model resources, reagents, biomarkers, new technologies, equipment, information databases, and modeling/calculation tools used in metabolic, cardiovascular, bone, skeletal muscle, and skin research.

- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, and cellular biology) to understand the metabolic, endocrine, cardiovascular, renal, bone, skeletal muscle, and skin disease complications associated with HIV infection and treatment.
- Support the development of new and improved research techniques to address the emerging metabolic, endocrine, cardiovascular, renal, bone, skeletal muscle, and skin complications in HIV-infected populations.
- Integrate metabolic, endocrine, cardiovascular, renal, bone, skeletal muscle, and skin studies into ongoing and planned treatment trials and observational studies.
- Link advances in understanding the immune response to HIV with changes in lipid, glucose, bone metabolism, muscle wasting, skin disease, endocrine parameters, and cardiovascular disease.

OBJECTIVE–E: *Pathogenesis of Malignancies*

Elucidate the etiologic factors, cofactors, pathogenesis, and consequences of HIV-related malignancies in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Elucidate the fundamental immune defects in HIV infection that predispose to the development of AIDS-defining and other malignancies that are associated with HIV infection.
- Identify the mechanisms by which immune dysfunction, oncogenes, suppressor genes, carcinogens, and non-HIV viral and other microbial genes and proteins contribute to the development of cancer and preneoplastic lesions in the context of HIV infection and HIV-associated malignancies; correlate these molecular factors with epidemiologic studies.
- Conduct studies on the biology of opportunistic pathogens that are the principal etiologic agents for HIV-associated malignancies (e.g., Kaposi's sarcoma-associated herpesvirus [KSHV]) and investigate their interaction with the host, and the mechanisms by which they cause malignancy in HIV-infected populations.
- Address the impact of HIV infection and prior therapy on the pathogenesis and treatment of common non-AIDS-related cancers (e.g., breast, colon, lung, prostate, etc.) that may emerge in the aging HIV-infected population.
- Identify the host factors that increase the risk of HIV-associated malignant disease in HIV-infected individuals.
- Investigate the contribution of HIV-associated or opportunistic-pathogen-associated inflammatory pathways and immune dysregulation to cancers whose incidence is increased in HIV-infected individuals.
- Determine the impact of AIDS-associated malignancies on the immune response to HIV.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related malignancies, and evaluate how the development and the manifestations of HIV-associated malignancies are altered by such therapies.
- Explore the mechanisms involved in the shift in the spectrum on both AIDS-defining and emerging non-AIDS-defining malignancies occurring in HIV-infected individuals treated with ART.
- Determine the impact of AIDS-associated malignancies on the immune response to HIV.

- Determine factors associated with clinical response and lack of response to antineoplastic therapeutic intervention in HIV-infected subjects.

To facilitate the research goals listed above:

- Promote programs to facilitate the development of and augmented access to *in vivo* animal models, patient specimens for HIV-associated malignancies, sharing of key patient samples, laboratory reagents, new technologies and equipment, information databases, and quantitative virologic and immunologic assays.
- Foster collaborative research between HIV and cancer researchers.
- Promote the collection of cancer specimens that occur in HIV-infected individuals, in different geographic locations in domestic and international settings.
- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, and cellular biology) to understand the etiology and pathogenesis of AIDS-related malignancies.

OBJECTIVE–F: *Pathogenesis of Neurological Disease*

Elucidate the mechanisms and consequences of HIV-associated neurological disease and neurobehavioral dysfunction in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Determine the cellular and molecular mechanisms involved in HIV-associated neurobehavioral and neurological dysfunction, and peripheral neuropathies, including:
  - identifying how HIV enters, establishes infection in specific cells and regions, spreads, and persists in the central nervous system (CNS);
  - investigating the connection between blood-brain barrier dysfunction, immune cell trafficking, and neuronal injury in the context of HIV infection;
  - determining the relationship of virologic (including distinct subtypes of HIV and acute infection), host (including the genetics of the virus/host interactions, blood-brain barrier dysfunction, and neuronal injury), pharmacologic, substance abuse, and environmental factors to susceptibility of neurological disease and HIV-associated neuropathogenesis;
  - investigating mechanisms of neuropathogenesis in the acute and early phases of infection, including reversible and irreversible changes in neuronal function and neuronal-glial communication that lead to CNS manifestations of disease;
  - determining the consequences of the biological activity of cytokines, other mediators, and their receptors on the neurologic tissue in the context of HIV infection; and
  - developing methods to monitor the levels of HIV replication and consequences of HIV infection within the CNS of living subjects.
- Determine factors associated with clinical response and lack of response to therapeutic interventions for neurologic and neurobehavioral complications of HIV disease.
- Determine the host and viral factors influencing independent evolution of drug-resistant HIV strains in the CNS compartment as well as its functional consequences.
- Determine the impact of HIV infection of CNS on systemic disease progression.
- Determine the role of the CNS as a reservoir of, and sanctuary for, persistent HIV infection.
- Define mechanisms of immunologic control of HIV, OIs, and coinfections in the CNS.

- Investigate aspects of HIV infection that uniquely influence the developing nervous system or the processes of neurocognitive decline with aging.
- Define mechanisms of immune reconstitution syndrome in the CNS in the setting of OIs and coinfections.
- Delineate the role of OIs, coinfections, other disease complications, and drug treatment in neurologic and neurobehavioral complications of AIDS including CNS dysfunction and peripheral neuropathies.
- Employ therapies that effectively suppress HIV replication and/or stimulate neuroprotection to probe pathogenic mechanisms of HIV-associated neurologic diseases and neurobehavioral dysfunction; evaluate how the manifestations of HIV-associated neuropathogenesis are altered by such therapies.
- Determine the mechanisms regulating the changing/fluctuating symptomatology of HIV-associated nervous system disease in the current era of ART.

To facilitate the research goals listed above:

- Develop and employ appropriate animal models (e.g., NHP models) of CNS HIV/SIV infection that best reflect specific aspects of the human HIV infection of CNS disease course on treatment that are crucial to understanding neurobehavioral and neurologic disorders.
- Develop methods to investigate, diagnose, and monitor HIV-associated neurological and neurobehavioral disorders in a range of populations including the developing world.
- Ensure that information, materials, and specimens needed for neuro-AIDS research are appropriately collected, catalogued, classified, stored, and distributed, and promote access to and sharing of new technologies and equipment.
- Encourage new multidisciplinary approaches to investigate HIV-associated neurological disease and neurobehavioral dysfunction.
- Improve existing and develop new technologies for biochemical markers and the imaging of neurologic dysfunction.
- Facilitate the translation of new insights from structural biology, computational biology, epigenetics, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, and cellular biology) to understand HIV-related neurologic disease.
- Integrate neurologic studies into the design and conduct of observational studies and treatment trials.

OBJECTIVE–G: *Pathogenesis of Organ/Tissue Disorders*

Elucidate the etiology, pathogenesis, and consequences of HIV-related organ-specific disorders in diverse populations across the spectrum of age and gender in national and international settings.

(The scientific objectives C through G are of equal weight.)

STRATEGIES

- Investigate the etiologic and pathogenic mechanisms and consequences of HIV-related:
  - gastrointestinal (GI), including intestinal, liver, and biliary, diseases,
  - nephropathy,
  - hematologic disorders,
  - pulmonary disorders,
  - autoimmune disorders,
  - cutaneous disease,
  - bone disease,
  - adipose dysfunction,
  - oral disease, and
  - other organ/tissue-specific disorders.
- Determine the consequences of aging on the pathogenesis of the above disorders.
- Employ therapies that effectively suppress HIV replication to probe the pathogenic mechanisms of HIV-related organ/tissue-specific complications, and evaluate how the manifestations of HIV-related organ/tissue-specific complications are altered by such therapies.
- Determine factors associated with clinical response and lack of response to therapeutic interventions against HIV-related disorders.
- Employ animal models to investigate the etiology and pathogenesis of HIV/SIV-associated disorders in the above systems.

To facilitate the research goals listed above:

- Facilitate the translation of new insights from structural biology, computational biology, and systems biology (multiscale modeling and commonly used approaches to validate hypotheses such as genomics, proteomics, and cellular biology) to understand the etiology and pathogenesis of HIV-related disorders.
- Integrate studies of HIV-related disorders in the design and conduct of treatment trials and observational studies.

CHAPTER 2

Prevention Research

Microbicides

Vaccines

Behavioral and Social Science

Microbicides

AREA OF EMPHASIS
Microbicides

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Basic Mechanisms of Mucosal Transmission*

Elucidate basic mechanisms of HIV transmission (virus and host factors) at mucosal/epithelial surfaces that are important for the development of a microbicide-focused prevention strategy in diverse populations.

STRATEGIES

Basic Biological and Physiological Research Related to Microbicides

- Identify, investigate, and characterize new and understudied viral and host targets and kinetic sequencing of infection important for the transmission and early dissemination of HIV in the upper and lower female and male genital and gastrointestinal (GI) tracts.
- Develop exploratory techniques such as genomics and proteomics to better characterize the functions and secretomes of female and male genital and GI tract immune and mucosal/epithelial cells.
- Investigate the importance of innate and adaptive host defenses that protect against HIV transmission and acquisition, and explore strategies to harness these defenses to protect against HIV acquisition in the upper and lower female and male genital and GI tracts.
- Determine the impact of microbicides on innate and adaptive mucosal/epithelial defense mechanisms in the female and male genital and GI tracts.
- Study the interactions between microbicides and microbial ecology, population dynamics of the microbiome, and mucosal/epithelial secretions and surfaces.
- Study the impact of normal and abnormal microflora ecologies on innate and adaptive mucosal/epithelial defenses in the upper and lower female and male genital and GI tracts and on the susceptibility to the transmission and acquisition of HIV infection.
- Study the physiologic and physical changes that occur during intercourse and discern how they relate to the transmission or acquisition of HIV and the safety, efficacy, and acceptability of, and adherence to, microbicides.

- Study the effect of semen on the immunology, physiology, rheology, and structural integrity of the female and male upper and lower genital and GI tracts, and the impact on HIV transmission and acquisition.
- Determine the cells, secretions, and/or tissue types that serve as portals of entry and/or facilitate transport processes that support the subsequent spread to and dissemination of HIV/SIV (simian immunodeficiency virus) to the lymphoid and other reservoir tissue in small animal and primate models of infection.
- Determine the role of viral phenotype/genotype/clade/resistance patterns in microbicide activity and delineate their relative effect on the efficiency of transmission of cell-free and cell-associated virus in secretions and tissues in the upper and lower female and male genital and GI tracts.
- Determine the mechanisms by which genital and GI tract inflammation, adaptive and maladaptive immune responses, and infections (including sexually transmitted infections [STIs]) influence HIV transmission and early propagation and dissemination of virus to lymphoid and other tissue reservoirs.
- Investigate the effect of variations in male and female endogenous hormonal status throughout the life cycle and exogenous hormonal exposure (including oral, absorbable, and injectable contraceptives and hormonal treatment) on the susceptibility of the female and male upper and lower genital and GI tracts to HIV acquisition and spread.

OBJECTIVE–B: *Discovery, Development, and Preclinical Testing*

Support the discovery, development, and preclinical evaluation of microbicides alone and/or in combination.

STRATEGIES

Microbicide Development and Preclinical Studies

- Support the development, validation, and standardization of specific, sensitive, and reproducible methods to assess antimicrobial and spermicidal activities of microbicide candidates.
- Support the development, validation, and standardization of specific, sensitive, and reproducible methods and biomarkers for assessing and quantifying innate, adaptive, and maladaptive responses in mucosal/epithelial tissues, semen, and other secretions before and after the use of microbicides.
- Promote the development and validation of biomarkers and other methods to assess the safety and efficacy of microbicides, and to determine adherence to product usage and document the sexual activity of female and male participants in clinical studies.
- Support the development, validation, and standardization of *ex vivo* upper and lower genital and GI tract and foreskin explant and cell culture models of human or nonhuman primate tissue that might provide a useful approach to investigate the very early events in HIV or SIV/SHIV (chimeric simian/human immunodeficiency virus) transmission.
- Support the development, validation, and standardization of *ex vivo* upper and lower genital and GI tract and foreskin explant and cell culture models of human or nonhuman primate tissue that facilitates the evaluation of the activity and toxicity of microbicide candidates and the determination of safety profiles, including the susceptibility to infection.
- Validate and standardize existing nonhuman primate (SIV/SHIV) and small animal (HIV) microbicide safety and efficacy models.
- Support the development, validation, and standardization of new animal models, including primate and small animal transgenic and humanized models for HIV susceptibility that closely reflect the dynamics of sexual transmission of HIV and the potential safety and impact of microbicide use in humans.
- Support the development of animal models of HIV transmission in the presence of other STIs that may affect the safety and efficacy of microbicide products.
- Support and promote the development of new and novel models and assays to discover, develop, and evaluate microbicide candidates.

- Evaluate the efficacy of microbicides against a variety of HIV viral resistance types, subtypes, and clades.
- Develop exploratory techniques such as genomics and proteomics to identify novel candidate agents or targets for microbicide strategies.
- Facilitate the study of potential microbicide candidates for their effect(s) on innate, adaptive, and maladaptive immunologic and inflammatory parameters associated with HIV acquisition, transmission, and replication.
- Study the effect of microbicides used before, during, and after intercourse on the structural integrity of the upper and lower genital and GI tracts, and the impact on the risk for HIV transmission and acquisition.
- Support the study of preclinical, pharmacokinetic, pharmacodynamic, and acute, chronic, and extended exposure toxicity testing. This should include but should not be limited to genotoxicity, reproductive toxicology, and carcinogenicity studies of microbicide candidates. This may include the development of new methodologies and technologies to measure product concentration and activity *in vivo*.
- Investigate antiretroviral (ARV)-based microbicides used in HIV-infected individuals, including adolescents and young adults and males and females. Evaluate the development of resistance when microbicides are used alone to prevent HIV superinfection or in combination with ARVs that are used to treat HIV disease. Identify and study the correlates of increased risk for ARV resistance.
- Investigate the potential interactions between microbicides and the use of complementary medical therapies.
- Investigate the effect of variations in female and male endogenous hormonal status across the life cycle and exogenous hormonal states (including oral, absorbable, and injectable contraceptives and hormonal treatment) on the innate and adaptive and maladaptive immunity of the female and male genital and GI tracts and on microbicide safety and efficacy.
- Foster the development of methods to solve manufacturing and synthesis hurdles that may prevent the advancement of microbicides through the preclinical pathway, by providing support for early Good Manufacturing Practice (GMP) manufacturing design and scale-up.

OBJECTIVE–C: *Formulations and Modes of Delivery*

Develop and evaluate safe and acceptable microbicide formulations and modes of delivery, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, biologic, social, and behavioral sciences.

STRATEGIES

Microbicide Formulations and Modes of Delivery

- Develop microbicide formulations, and dosage and delivery systems suitable for the upper and lower genital and GI tracts, that reduce or eliminate tissue toxicity and trauma while maintaining product acceptability.
- Develop placebo formulations with rheological, physical, and chemical properties that are identical to their microbicide-containing counterparts.
- Identify and validate methods that improve the understanding of rheological and physical properties that provide optimal bioadhesion, biodispersion, retention, distribution, and tissue concentration of microbicide formulations prior to, during, and after intercourse in male and female upper and lower genital and GI tract compartments.
- Develop methods to measure local tissue, target cell, and systemic absorption following topical microbicide use, and relate this to microbicide safety, efficacy, and potency.
- Develop and incorporate culturally sensitive measures and mechanisms to assess the acceptability of microbicides and their mode of delivery in diverse populations of men and women, including adolescents and young adults, that can be used in exploratory clinical studies and phased clinical trials domestically and internationally.
- Conduct research on and develop and study methods to better understand the biological mechanisms and physiologic and biological changes that contribute to the safety, efficacy, and acceptability of microbicide formulations. This includes, but is not limited to, the interaction between the rheological and biophysical properties of the formulation and hormonal status, age, menstrual cycle, nature of sexual activity, concomitant use of sexual enhancement products, pregnancy, frequency of use, sexual arousal, and concomitant STIs.
- Develop, validate, and standardize methodologies to analyze the physical, biological, rheological, and chemical properties of microbicides, formulated as individual and combination products.
- Develop methodologies and supportive studies to evaluate product characteristics of microbicides (such as taste, smell, color, lubricity, texture, and other factors) that can affect acceptability and use of, and adherence to, microbicides in diverse populations of males and females, including adolescents and young adults, communities, and cultures, and for different types of sexual acts.

- Support the discovery and development of reference formulations with known safety and acceptability profiles that can be used as a starting point for optimization and production of microbicide delivery systems.
- Support the development of novel, alternative formulation strategies for microbicide delivery systems such as sustained release, absorbable, and other delivery systems that will enable coital-independent and extended delivery (days to weeks to months) dosing.

OBJECTIVE–D: *Conduct Microbicide Clinical Trials*

Conduct clinical studies of candidate microbicides to assess safety, efficacy, acceptability, and adherence in the reduction of sexual transmission of HIV in diverse populations of males and females, including adolescents and young adults, in domestic and international settings.

STRATEGIES

Clinical Trials of Microbicide Products

- Identify populations in domestic and international settings with sufficient size and HIV seroprevalence, taking into account the estimates of participant attrition, to meet the power threshold for the conduct of Phase I, II, III, IV, and accessory clinical studies.
- Optimize all phases of microbicide clinical study design and evaluation, including the use of standardized measures to ensure the validity and comparability of study outcomes.
- Conduct pre-Phase I and accessory clinical research to address the issues of safety, efficacy, and acceptability in Phase I, II, III, and IV microbicide studies.
- Using culturally informed methodology, conduct and evaluate novel approaches to recruit and retain male and female participants across the life cycle in Phase I, II, III, and IV microbicide clinical studies in domestic and international settings.
- Design and implement Phase I, II, III, and IV clinical studies within HIV-infected populations to evaluate the safety, efficacy, and acceptability of, and adherence to, the use of microbicide products.
- Design, develop, and implement Phase I, II, III, and IV microbicide clinical studies that address and evaluate the influence of variations in male and female endogenous hormonal status across the life cycle and exogenous hormonal exposure on the safety, efficacy, and acceptability of, and adherence to, the use of candidate microbicide products.
- Identify, develop, and validate behavioral markers to evaluate the safety, efficacy, and acceptability of, and adherence to, microbicides, including the design, development, and evaluation of tools that measure product use and acceptability within and outside the clinical study environment. These tools should be adapted for applicability to female and male and adolescent and young adult populations.
- Address ethical issues in the design and conduct of microbicide clinical studies, including methods to enhance communication with community stakeholders and to evaluate and improve the informed consent process for participants.

- Address the ethical-legal challenges inherent in adolescent participation in HIV prevention intervention research, including geographic variation, and issues related to the age of consent/assent, decisionmaking capacity, right to autonomy, and local legal definitions of statutory rape.
- Conduct research on the acceptability and efficacy of microbicide candidates, used alone and in combination with other behavioral, preventive, and therapeutic methods used to prevent HIV. Compare these outcomes to non-microbicide-based approaches to HIV prevention.
- Implement novel translational research strategies to develop criteria for the movement of microbicide agents from preclinical animal studies to Phase I human trials.
- Identify and develop improved techniques to evaluate the safety and efficacy of microbicides applied to genital, GI, and other mucosal/epithelial surfaces of participants enrolled in clinical studies.
- Conduct followup research with participants who have seroconverted during the course of microbicide clinical studies in order to assess the impact of long-term product use and the effect of the product on contraception, pregnancy, and the acquisition of STIs and other coinfections.
- Study microbicide products in HIV-infected participants to determine the impact of product use on the development of superinfections, on reinfections, the progression of coinfections, and on drug resistance, drug interactions, and the potential for other adverse events.
- Design, implement, and evaluate Phase IV postmarketing surveillance studies on microbicides.

OBJECTIVE–E: *Conduct Microbicide Behavioral and Social Science Research*

Conduct basic and applied behavioral and social science research to inform and optimize microbicide development, testing, acceptability, and use in domestic and international settings among diverse populations of males and females, including adolescents and young adults.

STRATEGIES

Social and Behavioral Science Research Related to Microbicides

- Support the development and study of epidemiological models of risk and protection within community, social, and cultural contexts, to inform research on and the implementation and evaluation of microbicide use.
- Conduct behavioral and social science research on individuals, their partners, and communities at the onset of microbicide use and assess the influence of behavioral and social factors on the continuation or discontinuation of product use.
- Conduct behavioral and social science research, including community-based research on methods to improve adherence to microbicide products with varied formulations and to research protocols during clinical studies.
- Develop and evaluate the efficacy of behavioral and social interventions to enhance correct and consistent use of microbicide products in diverse populations and in different settings.
- Develop and evaluate the efficacy of behavioral interventions aimed to reduce sexual risk behaviors among participants in microbicide studies.
- Support operations research on the implementation and costs of behavioral interventions designed to support microbicide use, including studies of implementation, acceptance, sustainability, and dissemination.
- Improve current methods and develop new and improved tools for behavioral and social science microbicide research. These should include, but are not limited to, enhanced survey methods; the collection of valid self-report and other data; the collection of data on short- and long-term behavioral change and measurements of change over time, including disinhibition of sexual risk behaviors; the documentation and measurement of disease and other outcomes (including but not limited to the acquisition and progression of STIs and other coinfections, and seroconversion); and data on pregnancies that occur during studies.
- Improve current research methods and develop new tools for behavioral and social science research on microbicides, to inform techniques for the enhanced recruitment and retention of participants in Phase I, II, III, and IV clinical studies.

- Conduct behavioral and social science research on counseling strategies for females, males, and communities that addresses their different decisionmaking processes and ideas about the specific, optimal means for the prevention of HIV acquisition during the variety of sexual activities that confer HIV risk.
- Conduct behavioral and social science research on the appropriate counseling of females, males, and communities that addresses how decisions are made about the use of other HIV-prevention methods while using a microbicide that is known to have partial efficacy.
- Use the tools and measures of behavioral and social science research to predict and evaluate potential trends in microbicide use and sustainability in at-risk populations of males and females, including, but not limited to, adolescents, young adults, and older age groups.
- Conduct behavioral and social science research to determine the predictors of sustained microbicide use in male and female at-risk populations across their life cycle.
- Evaluate the effects of individual, family, and community expectations for pregnancy and childbirth on the use or nonuse of spermicidal and nonspermicidal microbicides.
- Evaluate the effect of intravaginal, intrarectal, and other sexual practices and the use of natural and synthetic products for hygiene, lubrication, sexual enhancement, and other practices on HIV transmission and on the use and efficacy of microbicides.

OBJECTIVE–F: *Microbicide Infrastructure*

Establish and maintain the appropriate educational, physical, and human resource infrastructure needed to conduct basic, preclinical, clinical, behavioral, and social science microbicide research domestically and internationally among diverse populations of males and females, including adolescents and young adults.

STRATEGIES

Infrastructure

- Establish and strengthen training and infrastructure for the development of domestic and international institutional capacity for basic microbicide research, including studies that facilitate the discovery and development of new microbicide candidates and assays for discovery and testing. Establish and strengthen the infrastructure, training, and capacity required to advance microbicide candidates from discovery to clinical evaluation and clinical implementation.
- Establish clinical study sites and the infrastructure required for Phase I, II, III, and IV studies domestically and internationally, and coordinate with efforts of other domestic and international organizations to optimize the availability of resources and encourage harmonization.
- Identify site-specific gaps in basic science, biomedical, behavioral, sociological, ethical, clinical, regulatory, and administrative training and support in national and international microbicide research sites, and design strategies that respond to those needs.
- Provide microbicide research training activities to foster and develop the skills of national and international independent investigators.
- Support and fund the dissemination of microbicide-related discovery and development strategies that will assist the research process, including assay standardization and validation, to domestic and international investigators.
- Strengthen training and infrastructure for the development of national and international institutional capacity for microbicide research, including laboratory capability, appropriate study design, data management/analysis, operational support, physical and human resource infrastructure, and the development of high standards of conduct for clinical research.
- Ensure the collaborative involvement of national and international communities in the planning and implementation of microbicide research.
- Foster and support the development of pilot and large-scale GMP production systems for the manufacture of microbicide agents and their formulations.
- Develop and evaluate strategies to promote and sustain the involvement of local governments, researchers, communities, and advocacy groups in the identification of priorities for the

development and conduct of basic, clinical, behavioral, and social science research and strategies, and in the maintenance of participants in research projects.

- Develop and evaluate strategies to encourage community participation in research and facilitate community acceptance of microbicides. Develop and evaluate appropriate communication strategies for affected communities in the process of testing candidate HIV microbicides, and prepare for the eventual integration of these products into domestic and international comprehensive prevention and care programs.
- Study the impact of regional ethical, legal, and regulatory challenges on the conduct of microbicide research with adolescents at risk for HIV.
- Foster interactions in the form of public and private partnerships to integrate NIH microbicide activities with external organizations to facilitate the cost-effective use of available resources and accelerate microbicide development.
- Foster collaborative partnerships between established investigators and between established and young investigators in the conceptualization, design, and conduct of microbicide research.

Vaccines

AREA OF EMPHASIS

Vaccines

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Host Defense Mechanisms*

Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

STRATEGIES

- Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other closely related lentiviruses by pursuing research in models that will provide information directly relevant to HIV infections; this includes the following areas of interest:
  - Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific (adaptive) and antigen-nonspecific (innate) cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
  - Define the structure-function relationships and the antigenicity and immunogenicity of HIV envelope proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active T-cell immunity and protective antibody.
  - Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structural analysis of envelope to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and closely related lentiviruses evade or escape from humoral and cellular immune responses; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
    - Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by major histocompatibility complex (MHC) class I and class II molecules. Investigate the interaction of HIV proteins with antigen-processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.

- Study the role of DCs in the induction of immunological memory and long-term protective function of different subsets of human lymphocytes in HIV-related disease and in response to vaccination.
- Define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and viral antigens of closely related lentiviruses, and development of long-term protective immunity, particularly in human subjects.
- Study the mechanism of action of vaccine adjuvants for HIV immunogens that enhance HIV/SIV (simian immunodeficiency virus) antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out comparative translational research in nonhuman primate (NHP) and human vaccines.
- Determine how chronic infection with one strain of HIV or closely related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain. Define the properties of the virus and of the immune responses that are responsible for lack of disease induction by attenuated viruses and/or protection from challenge with related pathogenic virus, and determine the protective mechanism, duration, and extent of cross-protection.
- Define the heterogeneity of specific responses to vaccine immunogens, specifically those derived from HIV, SIV, and SHIV (chimeric simian/human immunodeficiency virus), within diverse tissue compartments, and identify factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral exposure.
- Determine which factors promote development of particular human anti-HIV effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific innate protective mechanisms.
- Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes); study clinical samples from human volunteers participating in HIV vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.
- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.

- Seek new clues for correlates of immune protection and vaccine design by studying HIV-infected or highly exposed but seronegative individuals, across the lifespan, and SIV or SHIV NHP lentivirus models by conducting the following research:

- Study acutely HIV-infected individuals, exposed/seronegative, or possibly transiently infected humans (including uninfected children born to or breastfed by HIV-infected mothers, individuals with controlled therapy interruptions, HIV-infected individuals vaccinated with therapeutic vaccines while on antiviral therapy, and nonprogressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) or host factors that enhance or reduce the amounts of circulating virus and influence disease course.

- Elucidate the functional mechanisms for protective immunity against HIV, SIV, and SHIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.

- Investigate the sequence of events required for mucosal transmission/infection of HIV, SIV, or SHIV at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.

- Study mucosal immunity to HIV and SIV antigens and other infectious pathogens being used as HIV vaccine vectors in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.

- Acquire clinical specimens from populations relevant to HIV vaccine trials for laboratory studies; explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1 and their relationship to class I and class II MHC alleles; and define constraints on HIV evolution under immune selection pressure so as to guide vaccine development. Acquire appropriate, linked, epidemiological information to optimize interpretation of these analyses.

- Explore genome-wide association studies, in addition to targeted genetic analyses, to reveal novel viral protection/control mechanisms, particularly those that might be manipulated or inform HIV vaccine studies.

- Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, human papillomavirus (HPV), and other infectious diseases, and with administration of drugs of abuse or effects of antiretroviral therapy (ART) on HIV shedding in vaccinated subjects. Model these confounding elements in NHP.

- Develop *in vitro* experimental approaches for analysis of HIV vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across lifespan) and animals protected against SIV or SHIV by undertaking the following research activities:

- Develop and improve NHP animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible NHP models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by a genetic sequencing, particularly of selected regions of the macaque genome.

- Develop improved methodologies and assays to measure HIV neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary HIV isolates.

- Develop and standardize immunological reagents for HIV vaccine trials; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, storage, recovery, viability, shipping, and tracking of samples that will be essential in large-scale HIV vaccine trials.

- Study the function of HIV/SIV-specific CD4 T cells, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary HIV isolates; and make available those reagents required for HIV vaccine-related studies.

- Develop or improve sensitive quantitative measures of HIV (and SIV) in body fluids and low-level tissue reservoirs, including genital secretions and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

OBJECTIVE–B: *Vaccine Design, Development, and Animal Testing*

Design HIV antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other Government agencies, nongovernmental organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations such as breastfeeding infants, adolescents, and women.

STRATEGIES

- Multiple parallel approaches to development and testing of candidate HIV/AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:
  - Support the design, development, production, and testing of novel HIV/AIDS vaccine candidates for safety and for their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
    - Virus-like particles containing one or more virus proteins, peptides, or antigens;
    - Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
    - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
    - DNA or RNA coding for viral proteins;
    - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
    - Viral replicons or other immunogen strategies designed to target DCs;
    - Recombinant HIV envelope protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear or conformational structural epitopes for induction of effective antibody responses;
    - Structurally constrained HIV envelope fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and
    - Cell surface components carried on the viral surface.

- Foster collaboration between academic investigators, industry sponsors, the NIH, the Food and Drug Administration (FDA), other Government agencies, and NGOs on research and development of novel vaccine design concepts. These collaborations should:
  - Enable production of pilot lots of HIV vaccine candidates for testing in NHPs and human subjects. Where necessary, the NIH will provide products produced under clinical grade Good Manufacturing Practices (cGMP) and ensure that products meet these standards;
  - Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
  - Develop infrastructure; address scientific, legal, ethical, and regulatory issues to foster and encourage participation by, and collaboration among, academic investigators, industry, affected communities and populations, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- Foster the development of HIV vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production, stability, and ease of administration. This may include:
  - Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different arms of the immune response; and
  - Multivalent vaccine candidates incorporating different genetic clades and/or antigenic types to increase the breadth of immune responses.
- Support HIV vaccine design and development, incorporating methods to improve or modulate vaccine-elicited immune responses (qualitatively or quantitatively), including:
  - Novel adjuvants and delivery methods that might enhance effective DC presentation of HIV/ SIV antigens;
  - Agents that stimulate or modulate mucosal immune responses to HIV or other host defenses, including cytokines or chemokines;
  - HIV/SIV vaccines formulated with cytokines or incorporating cytokine genes or other biologically active molecules in vectors to improve the avidity of T cells and/or the functional activity of antigen-specific T cells; and
  - Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on HIV vaccine responses.
- Evaluate the efficacy of HIV/SIV vaccine and other immune prevention strategies in NHP animal models of HIV and closely related lentiviruses by:

- Testing HIV/SIV vaccine and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
- Determining *in vitro* correlates of an *in vivo* protective immune response generated by HIV/SIV vaccines;
- Determining the effect of HIV/SIV vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious SIV or SHIV challenge on the effectiveness of the vaccine-induced immunity;
- Defining the impact of different HIV/SIV vaccine approaches on the kinetics of immune responses, kinetics and localization of viral replication, including long-term followup of disease progression in the presence of low-level chronic infection and concomitant diseases (e.g., TB, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
- Determining the impact of genetic factors, age, and concurrent prophylactic antiretroviral therapy or topical microbicides on HIV/SIV vaccine responses and on protection against virus at various challenge sites; and
- Studying the efficacy of the HIV/SIV immune response in the face of viral variation.

- Investigate HIV/SIV vaccines and other biomedical prevention strategies with attention to potential factors such as integrity of the mucosal surface, changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormone replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune responses and how inflammatory activity might compromise integrity of the mucosal surface or the inductive ability of HIV vaccines.

- Support development of reagents and standardized methods to assess specific HIV or SIV vaccine-induced immune responses in NHP animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
  - Developing and refining assays to distinguish between serological and cellular responses due to immunization versus those due to HIV, SIV, or SHIV infection;
  - Characterizing and evaluating potential negative side effects of candidate HIV/SIV vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in NHP animal models;
  - Standardizing and validating assays to assess potency of candidate HIV vaccines;
  - Standardizing and validating assays to be used as Phase III study endpoints; and

- Abiding by Good Laboratory Practice (GLP) regulations to perform endpoint assays in support of product licensure and instituting quality assurance programs to assure sponsors and vaccine manufacturers that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with regulations stated in 21 CFR Part 58 and Part 11.

- Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development:
  - That are produced utilizing human-derived tumor cell and other continuous cell lines;
  - That utilize vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;
  - That might have the ability to be generated as either replicating or nonreplicating vectors;
  - That have the potential to cause autoimmunity or suppression of immunity, or to generate highly immunogenic antivector responses;
  - That might have the ability to increase the risk of HIV infection through vector-specific activation of T cells; or
  - That express potentially harmful vector proteins.

OBJECTIVE–C: *Active and Passive Pediatric Vaccines*

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

STRATEGIES

- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies need to be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
  - Develop relevant NHP animal models of maternal-fetal and maternal-infant perinatal transmission of HIV/SIV/SHIV that can:
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in pregnant and newborn primates;
    - Determine safety of various monoclonal and polyclonal antibody preparations against HIV;
    - Determine the best immunization routes or protocols to induce antibodies to HIV in milk and other secretions;
    - Evaluate infant cellular and humoral immunity to HIV in the context of breastfeeding from an HIV-infected mother, and determine immune correlates of protection for potential exploitation in vaccine strategies;
    - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breastfeeding HIV transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
    - Evaluate the effect of ART in combination with immune and behavioral prevention strategies.
  - Determine virologic and nonimmunologic/genetic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes:
    - Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and what additional viral factors are associated with differences in perinatal transmissibility;

        - Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervicovaginal secretions and in breast milk to determine their potential relevance in mother-to-child transmission (MTCT); and

        - Determining if HIV in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.

    - Identify maternal and infant immune responses that might control HIV replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.

- Define immune approaches that will provide specific and sustained protection against HIV/SIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:

    - Determine specific immune strategies for perinatal intervention that blocks interaction of HIV/SIV with its receptors and coreceptors and/or that targets infected cells.

    - Characterize the transmitted viral strains and monitor changes that may occur in proposed HIV vaccine trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.

    - Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among both HIV-infected pregnant women and newborns exposed *in utero* and intrapartum to HIV (born to HIV-infected women) as well as breastfeeding infants.

- Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in international settings with high seroprevalence. This testing includes the following activities:

    - Identify and characterize the important issues to consider in the development of criteria for advancement of candidate HIV vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children. These criteria may include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children.

    - Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic HIV vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).

- Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate HIV vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
- Develop criteria to define infant HIV infection status as a perinatal intervention trial endpoint in countries where breastfeeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
- Study HIV isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
- Study the impact of early ART interventions and HIV vaccines given while on effective ART, on the maintenance or regeneration of naïve T cells and antiviral immune responses in HIV-infected infants.

OBJECTIVE–D: *Conduct Phase I, II, and III Vaccine Trials*

Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate HIV vaccines or concepts in domestic and international settings.

STRATEGIES

- Support the conduct of Phase I, II, and III HIV vaccine clinical trials that will determine short- and long-term safety; immunologic responses measured by a broad range of humoral, cell-mediated, and mucosal immune parameters; and the efficacy of different preventive vaccine candidates. This includes the following:
  - Develop and implement strategies to coordinate studies in NHP with clinical trials so that data from NHP studies inform decisions about clinical trials and data from clinical trials can be used to improve NHP animal models.
  - Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should determine safety, test immunogenicity of vaccine concepts, and address questions about optimal vaccine strain/gene insert selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. Trials also should include an appropriate representation of the general populations (gender, age, ethnic and racial minority), particularly including understudied populations affected by HIV such as women and adolescents, and should be of an appropriate size to provide data on the frequency, magnitude, and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger test-of-concept (TOC) or efficacy trials.
- Develop a comprehensive plan for conducting HIV vaccine trials with rapid accrual, high retention, and adequate long-term followup of vaccinees to reach predefined endpoints, as follows:
  - Conduct research into methods to effectively recruit and retain diverse populations into HIV vaccine trials.
  - Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, the immune correlates of protection, long-term safety, behavioral factors that might influence adherence of followup visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
  - Conduct collaborative large-scale efficacy trials of preventive HIV vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by:
    - Evaluating HIV vaccine candidate efficacy against HIV infection, disease progression, and/or transmission;

- Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity against HIV;
- Ensuring that HIV vaccine trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of HIV disease, also including women and adolescents;
- Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
- Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, age (adolescents), and cultural backgrounds that will be involved in trials.

- Characterize the clinical course, detailed immune responses, and other characteristics of vaccinees (e.g., behavioral risk of infection) who become HIV-infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.

- Explore innovative trial designs to improve efficiency of HIV vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine or utilizing initially concordant HIV-uninfected couples at high risk or discordant couples). This includes the following areas of trial design research:
  - Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression, clinical outcomes, and the benefit of long-term followup.
  - Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on TB and STDs.
  - Utilize information from trials of other biomedical and behavioral interventions to consider novel trial designs (including, but not limited to, factorial designs and cluster-randomized designs), and the timing and impact of data from other trials on HIV vaccine trial design and conduct.
  - Consider the impact of early ART on HIV infections in complex trial designs.
  - Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, II, and III HIV vaccine trials, particularly to vulnerable populations of women and adolescents, and assist in providing solutions.

- Conduct behavioral risk assessment research in appropriate subgroups during HIV vaccine trials, particularly with Phase II, TOC, and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in an HIV vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors in future trials or application of HIV vaccines.
- Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical vaccine research and HIV immunotherapeutic interventions to facilitate and expedite translation of basic research to clinical practice.

OBJECTIVE–E: *Research and Preparation for HIV Vaccine Trials*

Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other Governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of HIV vaccine trials, while balancing the prevention needs of the at-risk populations; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize feasibility of vaccine studies in appropriate cohorts or populations.

STRATEGIES

- Identify and develop potential domestic and foreign sites with a high HIV seroincidence and improve access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:
  - Track the course of the epidemic by applying newer epidemiologic tools for estimating the HIV incidence in various populations with documented high-risk behaviors in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and able participants in HIV vaccine trials.
  - Identify and address barriers to participation in clinical trials among all at-risk groups, so that all relevant populations, especially women and adolescents, are included in HIV vaccine trials.
  - Develop and apply new laboratory diagnostic tools, including rapid, point-of-care tools, that can be adapted for high throughput to detect, characterize, and amplify virus in blood and mucosal fluids from individuals with new HIV infections and allow distinction between vaccinees and infected individuals.
  - Analyze MHC genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of virus peak and set point, and disease progression.
  - Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected people representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.
  - Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international HIV vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials; development of laboratory infrastructure; standardization of assays and development of panels of geographic-specific reagents composed of local, indigenous HIV+ and HIV- samples as well as peptide reagents to serve as controls when validating and standardizing assays that will

be used in support of clinical trials in that region; and participation of trained personnel in studies related to the trial.

- Establish, build, and nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; consider and address community concerns and social issues, and ensure ethical conduct of HIV/AIDS vaccine efficacy trials. This includes the following:
  - For all HIV vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale and public health need for the study.
  - Develop mechanisms (including CABs) to engage in collaboration and to provide education and the means to inform communities about HIV vaccines on a continuing basis so that social as well as medical concerns are addressed; work to establish trust in the community through open discussions of scientific rationale, expectations, and concerns.
  - For international trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), the World Health Organization (WHO), the Joint United Nations Programme on HIV/AIDS (UNAIDS), and the Global HIV Vaccine Enterprise to prepare for, plan, and conduct HIV vaccine trials adhering to the highest ethical and scientific standards.
  - Support the education of local CABs and local institutional review boards on issues concerning the conduct of HIV vaccine clinical trials in their communities.
- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities (e.g., circumcision, microbicides, anti-HSV treatment, HPV vaccine, breastfeeding strategies) that might have a substantial impact on either the design or the conduct of an HIV vaccine trial. This includes the following research:
  - Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in one or more populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of HIV vaccine efficacy.
  - Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, unblinding, and retention strategies pertinent to the design and execution of a successful vaccine efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the HIV epidemic is expanding disproportionately.

- Identify and develop strategies to involve the populations with highest risk for HIV transmission in different communities; particular attention should be given to high-incidence populations of adolescents and young persons.
- Develop research that anticipates and addresses effectively the potential adverse or unintentional effects of biomedical advances in HIV prevention (e.g., vaccines, microbicides, rapid testing, etc.), including behavioral disinhibition or increases in risk behavior such as failure to use condoms in sexual encounters, which may offset gains in prevention.
- Collaborate with other U.S. Department of Health and Human Services (DHHS) agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine trials in hard-to-reach populations in domestic sites; collaborate with the U.S. Military HIV Research Program (USMHRP), the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and other organizations to develop vaccine trial sites in international settings.
- Evaluate the impact of community-based participatory research in the acceptability of HIV vaccine trials.
- Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual integration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where HIV vaccine trials are conducted.
- Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm.
- Determine optimal methods of achieving informed consent for HIV vaccine efficacy trials.

- Develop tools to enhance recruitment, training, and retention of new investigators and staff involved in conducting HIV vaccine research globally.

Behavioral and Social Science

AREA OF EMPHASIS

Behavioral and Social Science

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Preventive Interventions*

Develop, evaluate, and advance prevention interventions: Support research to develop, evaluate, and diffuse effective behavioral, social, environmental, and economic interventions to prevent HIV transmission and acquisition by reducing HIV-related risk behaviors and increasing protective behaviors, including implementation research and studies of "scaling up" effective interventions.

STRATEGIES

- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral, social, and structural interventions in different domestic and international settings and populations to reduce high-risk HIV-related sexual and drug-use behaviors and HIV transmission.
- Translate and apply basic behavioral and social science research to optimize the development of innovative and effective intervention strategies.
- Support new research to identify or adapt the active ingredients of efficacious, theory-based interventions for broader adaptation and uptake.
- Modify, adapt, or refine existing efficacious HIV prevention interventions to increase their potency, and also to make them more easily administered and used in the community.

Populations and Contexts

- Develop and test interventions targeted at HIV-infected persons to reduce sexual and drug-use transmission risk behaviors.
- Support intervention research that addresses the impact of alcohol and/or drugs on sexual encounters that may contribute to HIV transmission and acquisition.
- Continue development of interventions targeting at-risk populations (e.g., injection drug users [IDUs], other drug users, partners of drug users, street children, and men who have sex with men [MSM]), with particular emphasis on drug-use and sex-related risks.

- Continue development of interventions for persons with multiple mental and physical disorders.
- Support domestic and international intervention research on the HIV prevention role of programs designed to enhance healthy sexual development and protective behaviors (including avoidance of too-early or nonconsensual sex, abstinence from unsafe sexual behavior, and access to and use of barrier methods) throughout one's lifetime.
- Support interventions for populations that are currently at low risk or that perceive themselves to be at low risk for HIV infection, but that may be susceptible to engaging in high-risk behaviors (e.g., non-sexually active, non-drug-using adolescents; subpopulations of heterosexual men and women; and certain middle-aged and older populations).
- Support intervention research that addresses important contextual risk factors for disproportionately affected groups that continue to demonstrate high-risk behaviors. This research also should identify which public health applications most effectively attend to cultural contexts.
- Develop, test, and evaluate interventions that target individuals both within prisons and returning to society from correctional settings; strategies include increasing access to education, information, therapeutic care, substance abuse treatment, prevention services, and clinical trials.
- Develop, test, and evaluate interventions that make use of existing systems of care that serve at-risk populations but do not routinely provide HIV prevention services (e.g., primary care or mental health settings) or address limited aspects of HIV prevention (e.g., sexually transmitted infection [STI] clinics that address sexual, but not drug use, risks).
- Develop, test, and evaluate interventions that target individuals both within the military and returning to society from the military; strategies include increasing access to education, information, therapeutic care, substance abuse treatment, prevention services, and clinical trials.
- Support the capacity to develop rapidly domestic and international intervention studies in response to changes in the epidemic.

Effectiveness

- Develop, test, and evaluate interventions that target a range or combination of levels of social organization (i.e., individual, dyad, family, network, community, institution, and society) and that examine how these levels interact to affect HIV risk and protective behavior and HIV transmission in different cultural contexts.
- Support research to increase the effectiveness, as strategies of HIV prevention, of interventions already used in service delivery systems for high-risk populations, such as family planning interventions; drug and alcohol abuse prevention; and treatments for STIs, drug and alcohol abuse, and mental disorder.

- Conduct studies to identify key components of efficacious interventions to facilitate transfer, adaptation, and application of them.
- Support research in the United States and abroad to improve the transfer of effective HIV interventions among communities, particularly research on the adoption and adaptation of efficacious HIV interventions by communities (including studies of diffusion processes and the exchange of knowledge between service providers and researchers); this research includes study of the maintenance of effective interventions and assessment of the generalizability of interventions with diverse populations.
- Evaluate novel interventions identified as high priority by HIV community planning groups and other service providers.
- Support research on the long-term impact of HIV prevention interventions on individuals and communities (i.e., 5 or more years postintervention).
- Develop and test the efficacy of adaptive preventive interventions, in which different dosages of certain prevention components are assigned to different individuals, or within individuals across time, with dosage varying in response to the intervention needs of the individuals.

Systems

- Support research to understand and improve the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care (including care for substance abuse and other psychiatric disorders), family planning, and other social services that reduce HIV risk behaviors and HIV transmission.
- Support research to understand and improve prevention services' linkages, coordination, and integration with primary medical and dental care; drug, alcohol, and mental health treatment; STI treatment; reproductive health and family planning services; services for orphans and vulnerable children; and other social services.
- Support research on integrating HIV prevention interventions into addiction treatment settings, with emphasis on behavioral treatments, alone or in combination with pharmacotherapies, for both HIV-infected and uninfected patients.
- Support intervention research on strategies for improving the willingness and capacity of communities to adopt and sustain primary prevention interventions.

Methods

- Design and test behavioral interventions for relevant populations to increase recruitment, retention, and adherence to protocols for HIV prevention research, including trials studying prophylactic vaccines, access and use of HIV testing, microbicides, and other biomedical prevention methods.

- Encourage, where appropriate, the use of quasi-experimental designs and the evaluation of natural experiments in domestic and international HIV intervention research.
- Integrate behavioral, social, and biological measures to improve sampling, measurement of risk factors, and evaluation of outcomes, including measures of substance use, recent HIV infection, population-based outcomes (e.g., seroepidemiology), recent sexual exposure, and STIs, with the overall goal of increasing the reliability and validity of measurement and sampling in prevention research.
- Support behavioral intervention studies that include HIV seroincidence data and other biologic markers as outcome measures.
- Support development of new approaches for addressing "hidden" or "difficult to reach" populations in intervention studies.

OBJECTIVE–B: *Basic Behavioral and Social Science Research*

Conduct basic social and behavioral research on factors influencing HIV risk behaviors and on the consequences of HIV disease: Support basic social and behavioral research to strengthen understanding of the determinants, processes, and cultural and contextual issues influencing HIV-related risk and protective behaviors and the consequences and impact of HIV disease, including treatment for and management of HIV infection. This includes domestic and international research that examines the societal, community, organizational, social network, dyadic, and individual barriers to and facilitators of the adoption and utilization of effective preventive and treatment interventions across the life course.

STRATEGIES

Continuing Critical Areas

- Conduct basic research to better understand the impact of HIV therapeutic regimens on adherence to treatment for HIV and cooccurring infections, sexual risk behaviors, drug-related risk behaviors, and psychosocial adaptation (i.e., improved quality of life).
- Examine neurobiological mechanisms of motivation that underlie HIV risk behaviors.
- Define the applicability and limits of rational models of behavior versus models that address states such as sexual arousal or drug- or alcohol-altered cognitive processing that do not conform well to existing models.
- Develop new models of behavioral change that integrate biological, psychological, and social perspectives to explain and predict the adoption and maintenance of HIV risk and HIV protective behaviors among vulnerable individuals and understudied groups, both domestically and internationally.
- Support theory-building studies developed in the context of HIV prevention research, as well as study theories developed for other areas (e.g., drug and alcohol abuse prevention, family planning, sexual development, and interpersonal social skill development) to see how they inform HIV prevention research.
- Support research that can more closely monitor the HIV/AIDS epidemic and associated risk behaviors so that emerging needs for basic behavioral and intervention research can be identified.

Consequences

- Support research on the decisionmaking processes and behaviors of health care workers regarding the offering of HIV counseling, testing, and other prevention services, as well as the prescription of HIV disease treatments, to those in need of HIV services and care; investigate the relationships between the health care workers' decisions and those of patients, family members, and community members.

- Conduct research concerning the health and life course of children, including orphans, affected by HIV. This research should include early identification and assessment of affected children for physical, psychological, and social consequences.
- Identify the neurobiological, behavioral, cognitive, social, and economic consequences of HIV disease for HIV-seropositive individuals (including children), their support systems (e.g., partners, family members, and other caregivers), health care systems, and communities.
- Support research on the economic and social implications for retired and older individuals who provide support and care to younger family members or friends with HIV/AIDS and their dependents, including studies of the support systems that may be in place for such individuals.
- Support behavioral research to study end-of-life transition strategies for patients with AIDS and their caregivers.
- Support interdisciplinary research, involving behavioral and biomedical scientists, to determine the relationships among stress, mood disorders, immune system functioning, and HIV infection, and to examine the psychosocial and physiological factors affecting those relationships.
- Support studies on animal models of behavior and behavioral change relevant to HIV infection and prevention; in particular, conduct behavioral neuroscience and neuropsychological research to determine the brain/behavior changes associated with exposure to HIV, the effects of HIV exposure on social behaviors (e.g., mother-infant attachment and peer interactions), and behavioral changes in relation to comorbidities of HIV and substance use and addiction.

Prevention

- Study the acquisition and maintenance of HIV-related risk and protective behaviors associated with HIV transmission or progression in specific social and cultural contexts, such as the sexual dyad, peer groups, social and substance-using networks, families, and communities. This would include studies of HIV risk, transmission, and progression as related to cultural norms that affect disempowerment of and violence toward women.
- Study how HIV risk changes over time as a function of developmental and life-course events, such as adolescence, childbearing, marriage or entry into other committed partnership, divorce and separation, and aging.
- Conduct research on decisionmaking processes that relate to sexual and drug-related risk-taking across the life course.
- Support multidisciplinary research that investigates the biobehavioral and sociobehavioral determinants of sexuality, including processes of sexual and gender identity formation, as they relate to HIV risk.

- Conduct research on partner selection and relationship dynamics, including how partner choice, partner formation, relationship development, and partner stability change over the life course and affect HIV risk and HIV-related behavior; studies should examine psychological, cultural, and social factors that influence these phenomena. Interactions of alcohol/drug use with partner selection and demographic trends in partnering, as related to HIV risk, should also be addressed.
- Support multidisciplinary research that investigates biobehavioral and sociobehavioral determinants of injection drug use and the transition from noninjection to injection drug use as they relate to HIV transmission; such research may also include studies that investigate the relationship between any drug use and sexual risk behaviors.
- Conduct research on individual social and cultural differences in human sexuality that have an impact on the sexual transmission of HIV; such research may include studies that examine how sexual behavior is affected by substance use and abuse, sexual abuse or coercion, developmental processes, and the formation and dissolution of intimate relationships.
- Study the social, structural, cultural, and demographic factors (e.g., socioeconomic status, marital status, ethnicity, sexual identification, age, and gender) that influence HIV-related behavior.
- Support research to understand how and whether communities engage in HIV preventive interventions, including studies to determine how to better ensure the use of prevention research by communities and public health entities in the United States and abroad.
- Support research that investigates the impact of laws and policies on behaviors associated with HIV transmission and acquisition.
- Conduct research that identifies the social and behavioral factors affecting recruitment, retention, and adherence to prevention and treatment interventions, including clinical trials of HIV-related vaccines, microbicides, and therapeutics.
- Support behavioral and social research on the acceptability, initiation, and use of biomedical and barrier HIV prevention methods (e.g., condoms, microbicides, rapid tests, and vaccines), and determine their impact on adherence to risk-reduction guidelines.
- Support behavioral and social research on the acceptability, initiation, and use of methods for HIV screening, counseling, and testing, and determine their impact on adherence to risk-reduction guidelines.
- Support basic and preintervention research on behavior modification and maintenance of new behavioral patterns for developing prevention and intervention strategies.
- Support behavioral surveillance research that measures changes, especially as a function of the diffusion of information and Internet use, in norms, attitudes, and expectancies regarding behaviors associated with HIV transmission and acquisition.

- Support research to identify how alcohol use (e.g., binge drinking trends) affects HIV risk among selected age groups.
- Study factors that enhance or preclude partner notification and the impact of partner notification on HIV testing and risk reduction.

OBJECTIVE–C: *Consequences of HIV*

Conduct treatment, health, and social services research for people infected and affected by HIV: Support research into the development, evaluation, diffusion, and adoption of strategies to increase early identification of HIV infection; to improve treatment adherence; and to prevent or minimize the negative physical, psychological, cognitive, and social consequences of HIV infection, including stigmatization of persons with or at risk for HIV infection. Support research strategies for promoting effective health care utilization among all persons with HIV infection and for promoting modifications in the health care delivery system to develop more effective, socially appropriate, and culturally sensitive methods to better serve treatment needs of infected populations, both domestically and internationally.

STRATEGIES

Treatment and Care

- Develop and test interventions to modify the practice behaviors and decisionmaking processes of health care providers to improve the quality of screening, counseling, and treatment services for HIV-infected persons and persons at risk for HIV infection.
- Support research on adherence to treatment regimens, including studies on communication techniques to improve shared decisionmaking between health care providers and HIV-infected individuals, issues such as how and when to initiate, interrupt, or cease therapy, and behavioral strategies to manage symptoms secondary to treatment protocols.
- Promote research to identify and remove barriers to effective health care utilization among persons with or at risk of HIV infection, including barriers associated with fear and stigmatization that affect access, engagement, followup, and adherence to health and social services across the care continuum (e.g., early identification of HIV infection, testing and counseling, health-care-seeking behavior, adherence, case management, and home/hospice care) and across the life course (i.e., from childhood to old age).
- Develop and test interventions to increase recruitment, adherence, and retention in HIV/AIDS clinical trials and care by HIV-infected persons from all vulnerable populations, with special attention to developmental and life-course issues.
- Support health services research and evaluation research to determine the impact of changes in the health care delivery system on HIV/AIDS care.
- Support research to foster more effective participation in treatment planning, decisionmaking, and formulating advance directives by patients with HIV and their families.
- Support behavioral and social research on the acceptability, initiation, and use of methods for HIV screening, counseling, and testing directed toward seropositive persons, and determine

their impact on adherence to risk-reduction guidelines and entry to and initiation of appropriate care and treatment.

- Support research on the special factors affecting adherence in older patients and medical decisionmaking in care of older patients.

Biopsychosocial Consequences

- Develop and evaluate interventions to prevent the adverse psychological and social consequences of HIV infection and to assist HIV-affected populations in coping with HIV infections, maintaining quality of life, and avoiding engagement in HIV-related risk behaviors.
- Test interventions to address the neuropsychological, neurodevelopmental, and psychiatric sequelae of HIV infection.
- Develop and evaluate interventions to minimize the impact of stigmatization on HIV-infected persons, including on their decisions regarding treatment and quality of life.
- Test interventions designed to support formal and informal caregivers and family members of HIV-infected persons in order to prevent, for example, depression and burnout.
- Support research to enhance the quality of life and minimize the impact of pain, fatigue, physical symptoms, and treatment side effects and to integrate effective palliative care throughout the course of treatment for all people living with HIV and AIDS.

OBJECTIVE–D: *Research Methods*

Improve the quality of behavioral and social science methodology in HIV research: Support research to advance innovative quantitative and qualitative methodologies to enhance behavioral and social science on HIV prevention and care, and to address pressing ethical issues in the conduct of such research.

STRATEGIES

Measurement

- Develop improved methodologies for collection and analysis of quantitative and qualitative data—including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time—based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS.
- Develop and strengthen research instruments that are culturally and linguistically appropriate for subpopulations (e.g., HIV-infected children, the elderly, and prisoners) and that reflect age-appropriate concerns.
- Develop and refine techniques for measuring social networks associated with HIV transmission.
- Develop and refine techniques for studying use of the Internet and its association with HIV transmission.
- Integrate behavioral, social, and biological measures to improve sampling, measurement of risk factors, and evaluation of outcomes, including measures of substance use, recent HIV infection, recent sexual exposure, and sexually transmitted disease.
- Develop improved methods for the reliable and valid collection of sensitive information regarding sexual and drug-use risk behaviors.
- Where appropriate, develop and/or adapt innovative substance abuse assessment approaches, such as biomarkers and passive alcohol sensors, ecological momentary assessment approaches, interactive voice response technology, personal data assistants (PDAs) to monitor substance use, wireless keypad surveys, Web-based surveys, cell phones, palmtop-assisted self-interviewing, and audio-enhanced PDAs.
- Assess new methodologies for testing efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.
- Support research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use: self-report measures, HIV infection, and other disease outcomes such as other STIs and blood-borne diseases.

- Develop improved qualitative approaches to theory building and to measurement of HIV-related behaviors, behavioral change, and factors that influence behavior and behavioral change.
- Develop improved approaches to formulate, integrate, and analyze theories founded on qualitative and quantitative observations.
- Develop and refine outcome measures and indicators appropriate for the evaluation of social policy and the societal impact of HIV prevention and treatment interventions.

Modeling

- Develop and refine mathematical models for linking behavioral change interventions with a reduction in HIV transmission at different levels of seroprevalence.
- Improve methods for forecasting and modeling AIDS caseloads, health care needs, and health care utilization under different treatment and survival scenarios and for forecasting and modeling prevention services needs.
- Develop and refine models of potential efficacy of environmental-level (e.g., laws and policies) interventions for reducing HIV risk.

Design and Statistical Analysis

- Develop improved methods for sampling subpopulations (e.g., children, homeless persons, drug users, the elderly, and MSM of color) and spatial units (e.g., migration routes, drug or human trafficking routes, and political jurisdictions of interest), with particular attention to "hidden" or "hard to reach" populations.
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal studies of HIV-vulnerable and HIV-infected populations, including improved participant retention strategies; statistical methods for dealing with participant attrition, missing data, and nonnormal distributions; and methods for measuring and analyzing nonlinear patterns of behavior change.
- Foster the development and dissemination of design alternatives to the randomized controlled trial that permit cost-effective evaluation of intervention strategies at the individual, group, and community levels.
- Foster the development, maintenance, and use of shared databases that will enhance the ability to identify and detect significant interactions between and within a variety of behavioral domains and also to identify the role of behavioral actions as mediators of biological outcomes of importance in HIV research.

Ethics and Other Issues

- Evaluate the effects of legal and ethical constraints on methods of HIV research and service delivery, particularly among vulnerable or special populations.
- Use behavioral and social research methods to investigate factors associated with particular ethical and legal principles in research design (e.g., competence to provide consent, prevalence of adverse events, and associated remedies).
- Develop and refine research techniques to advance multisite, intercultural, and international studies.
- Encourage secondary data analysis; develop approaches to protect and document confidentiality.

CHAPTER 3

Therapeutics Research

AREA OF EMPHASIS

Therapeutics

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Discover and Develop Anti-HIV Treatments*

Identify and validate viral and cellular functions required for HIV replication that can be targeted for viral inhibition, clearance, and prevention of transmission. Discover and develop novel agents and therapeutic strategies directed against viral and host factors involved in HIV transmission, infection, replication, and persistence, and that are effective to prevent and treat drug-resistant virus. Encourage collaborations between academia, industry, private and public organizations, the community, and the NIH.

STRATEGIES

- Identify, characterize, and validate new and understudied viral and host targets for anti-HIV therapy (e.g., factors involved in viral fusion, entry, integration, transcription, replication, assembly, budding, infectivity, virulence, and pathogenicity). Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
  - Develop agents (including natural products) and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries.
  - Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
  - Develop new compounds and chemical formulations, and other methods, suitable for the gastrointestinal tract.
  - Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent and selective therapeutic agents and therapeutic vaccine candidates with activity against drug-resistant strains. Post lead structures on publicly available databases.
  - Integrate genomics and informatics paradigms, concepts, and methodologies (micro-chip-based screens and analyzers) into mainstream drug discovery and development of therapeutic entities and strategies.

  - Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; expand the infrastructure to provide services and reagents needed by the scientific community.

  - Evaluate the intracellular pharmacokinetics and activity of antiretroviral (ARV) agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.

  - Develop agents with desirable biopharmaceutical characteristics (e.g., improved bioavailability and tissue penetration to the central nervous system [CNS] and other sanctuaries); develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.

- Advance basic and applied gene-based strategies to treat HIV infection. Foster new approaches and technologies to optimize gene delivery that results in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.

- Develop therapeutic strategies, including approaches to identify patients in the early stage of HIV infection, with emphasis on the early T-cell depletion in the gastrointestinal tract.

- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.

- Study the effects of recombination within and between HIV clades on the evolution of drug resistance.

- Develop and evaluate interventions aimed at HIV-related chronic immune activation.

- Develop mathematical and computer models of HIV infection and therapeutic interventions that stimulate and predict *in vivo* efficacy, toxicity, and other outcomes of drug regimens and clinical trials. Investigate the use of pharmacogenetics in identifying optimum therapies.

- Investigate the host cell effects of ARV drugs.

- Develop and perform the preclinical evaluation of fixed-dose combination formulations of approved ARV drugs, including doses appropriate for children.

- Develop and evaluate pediatric drug formulations of available and new ARV drugs, with emphasis on low-dose dividable solid formulations appropriate for use in resource-limited settings, as well as liquid formulations.

OBJECTIVE–B: *Conduct Clinical Trials of Anti-HIV Treatments*

Assess the short- and long-term efficacy and effectiveness of therapeutic agents and strategies against acute or established HIV infection and transmission in treatment-naive and treatment-experienced HIV-infected individuals, across the lifespan, through the conduct of clinical trials and cohort-based studies (including the development of new clinical trial methodologies) in domestic and international settings, especially in resource-developing nations, and develop strategies to mitigate factors that adversely affect the success of therapeutic strategies against HIV infection. Develop domestic and international partnerships to design and conduct clinical studies where the epidemic is prevalent.

STRATEGIES

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults (including gender-based and genetic differences in special populations), adolescents, and children to determine pharmacokinetics, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
  - Evaluate optimal combinations of agents selected for antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
  - Evaluate optimal therapies and strategies for individuals who have acute or recent infection (including neonates/young infants with perinatal infection), chronic infection but no prior antiretroviral therapy (ART), and those with prior ART including individuals with multiple drug-resistant virus.
  - Support clinical trials to study:
    - long-term effectiveness (including toxicities) of therapeutic strategies;
    - timing, selection, and strategic sequencing of ARV agents to optimize clinical outcome;
    - optimal treatment for heavily ARV-experienced individuals with treatment failure; and
    - the effect of ART on HIV-related comorbidities.
  - Evaluate novel therapeutic modalities (e.g., cell-based, gene-based, and therapeutic vaccine approaches) with state-of-the-art antiretroviral therapies.
  - Evaluate coformulated ARVs in all age groups.
  - Investigate the effects of drug-sparing regimens on efficacy, resistance, and transmission.

Clinical Trials Enrollment

- Strengthen efforts and implement new approaches to ensure the enrollment and retention of specific populations, including women, children, adolescents, minorities, substance abusers, and older adults in clinical trials and cohort-based studies to reflect the incidence of the epidemic.
- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials and cohort-based studies that reflect the demographics of the epidemic. When appropriate, evaluate potential gender, race, ethnicity, age-specific, pregnancy-related, and nutrition-related differences in drug efficacy and safety, including pharmacokinetics, metabolism, tissue absorption, and drug elimination.
- Identify and test strategies to improve the recruitment and retention of individuals in clinical trials.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate surrogate markers in response to various therapeutic interventions, including those most applicable to resource-limited settings.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of ARV agents.
- Develop methodology to facilitate cross-protocol analysis and meta-analyses.
- Conduct research on how and why subjects decide to participate in clinical trials in order to increase enrollment and maintain adherence to study protocols.
- Improve research methodologies for the ethical conduct of clinical trials.

Pharmacology

- Determine the relationship between drug exposure (pharmacokinetics) and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management, including the utility of therapeutic drug monitoring and potential application of pharmacogenetics.
- Investigate drug interactions, including pharmacokinetic and pharmacodynamic impacts, among commonly used treatments for HIV-related disease and its complications, as well as other substances that may be used by HIV-infected individuals.
- Evaluate the effects of nutritional deficiency on the pharmacokinetics and activity of ARV drugs.

Viral Reservoirs

- Evaluate the presence and persistence of HIV in different tissue compartments during ART; investigate the role of anatomic and cellular sanctuaries in the development of HIV drug resistance, transmission, and establishment of long-term reservoirs.
- Evaluate the penetration of ARVs into different tissue compartments (e.g., genital secretions/semen, CNS, breast milk, gastrointestinal tract, etc.).

Viral Resistance and Fitness

- Explore the utility of real-time ARV phenotypic and genotypic assays in managing ART across a broad spectrum of individuals.
- Evaluate the impact of transmission of drug-resistant strains of HIV on disease progression or therapy.

Mechanisms of Viral Failure

- Identify and evaluate the viral and host factors, including human genomics, associated with ART failure, including drug interactions, drug resistance, drug toxicities, pharmacogenetics, malabsorption, and suboptimal adherence.

Adherence and Self-Management

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to facilitate better adherence to ARV regimens.
- Develop better methods to assess adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.
- Investigate strategies for managing symptoms that are attributed to therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens. This may include self-management or other combined biobehavioral approaches.

International

- Expand the development of international collaborations that will assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children, including studies on factors resulting in early deaths occurring within the first 3 months of treatment/care.
- Assist developing nations, as appropriate, in technology transfer through training, infrastructure, and capacity building to facilitate the evaluation of ARV agents and other therapies in local settings.

- Assess the barriers to delivery of effective health care for HIV disease including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop and evaluate simpler, reliable, user-friendly, and inexpensive surrogate markers, assay technologies, and rapid point-of-care diagnostics for monitoring immunologic and virologic status and ARV drug responses that can be used in resource-limited settings.
- Develop standardized clinical indicators to determine how and when to initiate ART, to monitor responses to therapy, and to determine when to change therapy.
- Determine acceptable laboratory monitoring for drug toxicity in resource-limited settings.
- Evaluate whether nutritional status (particularly chronic malnutrition) affects the efficacy of therapy and whether it affects the risk or severity of adverse events associated with ART.

OBJECTIVE–C: *Approaches to Manage Treatment-Related Complications*

Develop strategies to predict, evaluate, treat, and prevent complications of long-term HIV disease and toxicities of antiretroviral treatment and the interaction of comorbidities in HIV infection in domestic and international settings.

STRATEGIES

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection, particularly those complications unique to or prevalent in international settings.
- Evaluate potential delayed or late effects of ART following short-term administration of prophylaxis regimens (e.g., for prevention of mother-to-child transmission [MTCT]), as well as during chronic treatment.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials (i.e., meta-analysis between studies, efficacy of interventions in clinical trials versus effectiveness in public health practice).
- Support research on the pathogenesis and mechanisms of toxicity of drugs used to treat HIV disease.
- Develop and test approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which ART and/or HIV disease may affect metabolic processes.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, and bone studies into ongoing and planned treatment trials which may provide an opportunity to answer important questions related to potential complications of ART.
- Develop approaches to monitor and evaluate the effects of gender, race, age, pregnancy status, and type of exposure on complications of ART.
- Evaluate the impact of nutritional deficiencies, impaired access to safe drinking water, regionally significant coinfections, and other population- and area-specific factors on complications of ART in developing countries.
- Evaluate the impact of nutrition and nutritional interventions in undernourished populations or lactating mothers provided concurrently with ART on improved clinical outcomes.
- Evaluate drug interactions with potential clinical significance for HIV-infected individuals, particularly the pharmacokinetics and pharmacodynamics between ARVs and drugs used to treat HIV-related comorbidities or medications used in the treatment of drug addiction and mental disorders; develop strategies to avoid or minimize the clinical impact of these interactions.

- Evaluate factors associated with and ways to prevent immune reconstitution syndrome.
- Study the effects of treatment and long-term HIV disease on the natural aging process and vice versa, including development of comorbidities across the lifespan of the HIV-infected individual.

OBJECTIVE–D: *Prevent and Treat Coinfections (OIs)*

Develop and evaluate new agents and strategies for diagnosis, prevention, and treatment of the most significant coinfections in the context of HIV disease in domestic and international settings and across the lifespan of HIV-infected individuals, including tuberculosis (TB), malaria, hepatitis C virus (HCV), hepatitis B virus (HBV), human papillomavirus (HPV), Kaposi's sarcoma herpesvirus (KSHV), and Epstein-Barr virus (EBV). Develop and evaluate new therapeutic agents and strategies to prevent and treat drug-resistant coinfections, particularly TB.

STRATEGIES

Preclinical Discovery and Development

- Support preclinical drug design and development programs to develop therapies against associated pathogens and their disease manifestations, especially *Mycobacterium tuberculosis* (TB) (including multi-drug-resistant TB [MDR-TB] and extensively drug-resistant TB [XDR-TB]), malaria, HCV, HBV, HPV, KSHV/human herpesvirus (KSHV/HHV-8), EBV, and cytomegalovirus (CMV), with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics, as well as development of formulations appropriate for use in children.

- Support and encourage mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating the most significant coinfections; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.

- Cooperate with the private sector to increase involvement and investment in anti-opportunistic infection (OI) and anti-coinfection drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

- Support studies and develop vaccines and interventions for coinfections (e.g., TB, HPV, rotavirus) in HIV-infected children, adolescents, and adults.

Clinical Trials of Preventive and Therapeutic Regimens

- Assess the impact of new ARV regimens on the risks for and manifestations of infections associated with HIV disease in adults, adolescents, and children.

- Improve our understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.

- Improve strategies for prevention of multiple infections in the context of ART; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs and coinfections; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.

- Develop tools to identify HIV-infected individuals at high risk for development of specific OIs and coinfections, to improve the efficiency of clinical trial design and the risk/benefit ratio of the currently utilized drugs for prophylaxis and for treatment.
- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs and coinfections (particularly TB), quantitative assessment of microbiological responses, and drug sensitivity testing, including assays appropriate for use in children with coinfections.
- Support clinical trials in HIV-infected individuals, including children, of preventive and therapeutic regimens for HIV-related coinfections.

Coinfections

- Support research on the interactions between ART and treatments for coinfections.
- Study the interaction between HIV infection and infectious complications upon pathogenesis, presentation, and disease outcomes in adults, adolescents, and children.
- Support clinical trials, domestic and international, of adults and children coinfected with HIV and TB (both active and latent infection). Evaluate safety and efficacy of treatment regimens in coinfected individuals. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression.
- Investigate surrogate markers of TB disease that could distinguish between latent, active, and eradicated infection in coinfected individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Support clinical trials investigating the efficacy and risks of treatment of HCV in individuals who are coinfected with HIV; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Study the interaction of coinfections with HIV transmission (e.g., placental malaria and perinatal infection) and effects on HIV disease progression.

Pharmacology and Toxicology

- Conduct preclinical studies of anti-OI and anti-coinfection drugs (alone or in partnership with industry) to assess their immunologic, pharmacokinetic, pharmacodynamic, toxic, reproductive, and teratogenic effects, as well as transplacental carcinogenicity; develop pediatric formulations of anti-OI drugs, including lower dose solid as well as liquid preparations.
- Support clinical studies to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs and coinfections in HIV-infected infants, children, and pregnant women.

- Evaluate drug interactions between anti-TB agents and HIV medications. Support the investigation of new anti-TB agents with fewer side effects, drug interactions, and/or action against MDR- and XDR-TB.

Adherence and Self-Management

- Support research on the effectiveness of pharmacologic and other approaches in promoting adherence to anti-coinfection regimens.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-OI and anti-coinfection drugs appropriate for use in infants, children, and other populations.
- Develop and evaluate interventions to facilitate better adherence to therapies among populations with HIV infection and substance abuse and/or mental illness.
- Investigate strategies for managing symptoms that are attributed to HIV infection, coinfection, and/or therapy, and investigate the relationship between symptom management and improved adherence to ARV regimens. This may include self-management or combined biobehavioral approaches.

International

- Conduct clinical trials in adults and children to evaluate agents for the prophylaxis and treatment of HIV-associated OIs and coinfections; target infections shown to cause significant morbidity by epidemiologic studies, and made worse by HIV-induced immunosuppression.
- Develop and evaluate strategies for treatment and prevention of prevalent opportunistic and endemic infections in the context of HIV infection.
- Evaluate the role of nutrition, malnutrition, and severe malnutrition on treatment and prophylaxis regimens for OIs and coinfections.

OBJECTIVE–E: *Approaches to Interrupt Vertical Transmission*

Develop and assess strategies to prevent mother-to-child transmission (MTCT), applicable to resource-limited and -rich countries, with emphasis on strategies to prevent transmission through breastfeeding, the short- and long-term effects of interventions for preventing MTCT on the health of women and infants, and development of drug resistance after antiretroviral MTCT prophylaxis and its association with efficacy of subsequent ART in future pregnancies.

STRATEGIES

Mechanisms of Transmission

- Investigate the mechanisms and timing of MTCT to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Investigate risk factors (e.g., immune, viral, and host-related) associated with transmission of HIV through breast milk.
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk.

Interventions and Trials to Evaluate Interventions to Prevent Transmission

- Develop and evaluate strategies for preventing transmission of HIV from pregnant women to their offspring, and evaluate the impact of those strategies on maternal health treatment options; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, HIV vaccines, and adjuvants, alone or in combination.
- Develop safe and conveniently administered strategies to prevent MTCT using interventions that are affordable in resource-limited nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactational period.
- Evaluate the pharmacokinetics and safety of ARV drugs in pregnant women and their fetuses/infants, and the penetration of ARV drugs into breast milk and genital fluids.
- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum ART is not given or available (e.g., postpartum prophylaxis of the infant only).
- Support international collaborative efforts to conduct clinical trials of interventions to prevent MTCT.

- Study the effects of ARV regimens used for maternal health indications on preventing MTCT (including postnatal transmission through breast milk).
- Support research and development of new clinical trial designs, statistical methodologies and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the prevention of mother-to-child transmission.
- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum breastfeeding transmission of HIV, and to evaluate transplacental passage of ARV agents and their effects on placental function and on fetal development and viability.

Issues Related to Antiretroviral Drug Resistance

- Evaluate the effects of preexisting viral drug resistance in pregnant women on the effectiveness of ARV regimens to prevent MTCT.
- Evaluate the risk for the development of HIV variants with detectable antiretroviral drug resistance in pregnant women who receive different types of ARV prophylactic regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus in plasma, breast milk, and genital secretions.
- Evaluate the risk for development of HIV variants with detectable antiretroviral drug resistance in infants who become infected despite maternal receipt of ARV prophylaxis regimens and the kinetics and durability of such resistance in cell-free and cell-associated virus.
- Evaluate the effects of developing drug resistance following ARV prophylaxis on the health and response to future ART in women and infants who become infected with HIV despite prophylaxis.
- Evaluate the effects of drug resistance developing following ARV prophylaxis in an initial pregnancy on the efficacy of the prophylactic regimen in reducing transmission in subsequent pregnancies.
- Evaluate effective, safe, simple, and short alternative antiretroviral regimens that have lower risk of development of resistance in women or infants infected despite prophylaxis than those currently used for prevention of MTCT in resource-limited settings.
- Evaluate the public health impact of ARV resistance that develops in pregnant HIV-infected women secondary to use of ARVs solely for prevention of MTCT.

Issues Related to Short- and Long-Term Effects of ARV Prophylaxis for Reducing MTCT

- Evaluate the short-term toxicities, pharmacokinetics (including transplacental drug transfer to fetus/infant), and ARV activity of new agents, existing agents, and combinations of agents in pregnant HIV-infected women and their neonates.
- Evaluate whether pregnancy increases the risk of potential ARV toxicities, the pathogenesis of such toxicities in pregnancy, and clinical findings or laboratory assays that might be predictive of such effects.
- Study the effects of ARV regimens used during pregnancy for treatment of maternal HIV disease on maternal health and pregnancy outcome.
- Evaluate the optimal regimen(s) for preventing MTCT in women who are receiving ART for the sole purpose of preventing perinatal transmission, and short- and long-term clinical, immunologic, and virologic effects of receiving ART during pregnancy in such women who choose to discontinue ART after delivery.
- Evaluate the short- and long-term clinical, immunologic, and virologic effects in women who receive ART during lactation solely to prevent breast milk transmission, but who discontinue treatment following weaning.
- Evaluate the potential mechanisms for possible carcinogenic or mutagenic effects of *in utero* ARV exposure.
- Evaluate the pathogenesis of potential ARV toxicities (e.g., mitochondrial toxicity, bone toxicity) in uninfected, HIV-exposed infants with perinatal ARV exposure, and develop animal models or laboratory assays that might be predictive of such effects with exposure to an individual ARV agent alone or in combination with other ARVs.
- Develop better clinical algorithms and laboratory assays to diagnose/assess mitochondrial toxicity associated with ARV exposure in infants and children.
- Develop and implement feasible studies that assess the long-term effects of *in utero* and/or postpartum exposure to ARVs on both HIV-infected and -uninfected children, both domestically and internationally.

Implementation Issues

- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in developed and developing countries, including ways to increase availability and acceptability of prenatal HIV testing and of prophylaxis to prevent MTCT.
- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in developed and developing settings to permit the earliest possible

determination of HIV infection in infants, and whether ARV and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.

- Evaluate innovative methods, including rapid HIV antibody testing, to identify HIV infection in pregnant women with unknown HIV serostatus who present in labor, and to assess the acceptability of such testing and acceptability and efficacy of ARV prophylaxis to reduce MTCT, when administered to the woman intrapartum and her infant, or to her infant alone.
- Evaluate the public health impact of programs to prevent MTCT.

OBJECTIVE–F: *Therapeutic Approaches to Prevent Horizontal Transmission*

Evaluate the impact of antiretroviral and immunotherapeutic strategies and their roles in the prevention of horizontal HIV transmission (e.g., sexual, noninjection drug use, or injection drug use [IDU] transmission) in appropriate domestic and international settings.

STRATEGIES

Mechanisms of Transmission

- Evaluate the influence of drug resistance on the efficacy of ARV regimens to prevent sexual transmission.
- Use and/or develop suitable animal models and clinical studies to evaluate genital and anal passage of cell-free and cell-associated virus and ARVs.
- Evaluate the influence of systemic HIV treatment on viral shedding in the anogenital tract.
- Evaluate the impact of anti-STI (sexually transmitted infection) treatment on transmission of HIV and HIV shedding in the anogenital tract.

Interventions to Reduce Transmission

- Support domestic and international collaborative efforts to conduct trials of ARV, immunotherapeutic, and other treatment interventions with an endpoint of horizontal transmission in acute and chronic infection.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV-infected individual; such strategies may include ARVs, therapeutic vaccines, anti-HIV immunoglobulin, monoclonal antibodies, and immunotherapeutic agents, alone or in combination.

Issues Related to ARV Interventions

- Evaluate the risk for developing antiretroviral drug resistance (in cell-free and cell-associated virus, and in sequestered genital or anorectal sites) when using ARVs in interventions to reduce horizontal transmission, including the development of antiretroviral drug resistance in individuals who become HIV-infected while receiving such therapy or in HIV-infected individuals being administered such therapy solely to reduce horizontal transmission.
- Evaluate the public health impact of ARVs on reducing horizontal transmission.

OBJECTIVE–G: *Treatment of AIDS-Related Neurologic Disease*

Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system manifestations of HIV disease in domestic and international settings.

STRATEGIES

Preclinical Development

- Develop therapeutic agents to block HIV entry into the CNS and treat HIV infection in the CNS; develop and evaluate novel strategies such as neuroprotective agents that are active against putative pathways of HIV-induced CNS dysfunction in adults, adolescents, and children.
- Develop and utilize *in vitro* and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents (tailored for needs during neurodevelopmental and mature brain periods) for the nervous system complications of HIV infection.
- Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants.
- Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of HIV disease progression and treatment effects as they relate to the nervous system.
- Characterize the CNS pharmacokinetics and pharmacodynamics of ARVs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects.
- Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of ARVs into the CNS compartment.
- Develop better strategies including complementary and alternative medicine approaches to prevent, diagnose, and treat peripheral neuropathies and other CNS complications in HIV-infected individuals.
- Develop optimal therapies for pain management in HIV-infected individuals.
- Monitor CSF for HIV viral load and immune activation markers in individuals enrolled in studies of ART.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease.

- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Evaluate the effectiveness of reducing HIV-associated CNS disease burden by therapeutic agents currently used to treat other neurologic diseases (e.g., Parkinson's and Alzheimer's disease) that may share pathophysiologic features with HIV-associated neurologic disease.
- Assess the incidence and prevalence of HIV-1 and HIV-2 induced neurological and neurobehavioral complications, and assess the impact of other viral, bacterial, fungal, or parasitic infections on HIV disease in the CNS.
- Conduct viral genetic analyses of HIV derived from CNS sources (including studies of the role of HIV-1 non-B subtypes and HIV-2) in causing neurologic, cognitive, and neurobehavioral dysfunction.
- Determine anatomical, structural, and genetic contributors (haplotypes, epigenetics) to neurological vulnerability to HIV infection and related inflammatory processes.
- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications, with treatments for drug abuse and cooccurring mental health disorders; develop treatments and regimens that are optimized for HIV-infected individuals with comorbid depression and other psychiatric disorders.
- Develop adjunctive therapeutic agents that have not only immunomodulatory functions but also neuroprotective functions to reduce comorbid psychiatric conditions (markedly depression and anxiety disorders) in HIV-infected individuals.
- Develop novel or adapt existing rehabilitative strategies to ameliorate HIV-associated CNS disease manifestations that affect social-emotional, motor, sensory, cognitive, and daily functioning.

Clinical Neuroassessment, Methodologies, and Trials

- Design and support clinical trial studies addressing nervous system complications of HIV infection and treatments in adults, adolescents, and children.
- Improve existing and develop novel sensitive, reliable, and valid measures of neuropsychological performance and neuropsychiatric status having cross-cultural and international applicability and sensitivity to HIV-associated neurological complications and ARV treatment, including appropriate and standardized measures of neurodevelopment in children applicable to resource-limited settings.
- Determine the incidence and prevalence of HIV-associated neurologic disorders, primarily HIV-associated dementia (HAD), minor cognitive and motor disorders (MCMD), and peripheral neuropathy, in the context of long-term ART.

- Determine the effects of ART on neurodevelopmental function in HIV-infected children.
- Support the research and development of new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers, to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic and cognitive complications of HIV disease.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales in clinical trials that are aimed at measuring the impact of nervous system complications of HIV infection.

OBJECTIVE–H: *Treatment of AIDS-Related Cancers*

Develop and evaluate improved strategies for the assessment, treatment, and prevention of cancer-specific manifestations of HIV disease and antiretroviral therapy in domestic and international settings.

STRATEGIES

Preclinical Development

- Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles.
- Based upon structural, biologic, immunologic, and biochemical information, develop agents for the prevention and treatment of HIV-associated malignancies.
- Develop preclinical and *in vivo* models for testing potential therapeutic and preventive strategies against HIV-associated malignancies.
- Utilize emerging information on the pathogenesis of malignancy complications of HIV infection, including new viral agents, to develop new preventive, diagnostic, and therapeutic strategies for such tumors.

Diagnostic Methods

- Develop and improve methods for early diagnosis of malignancies in the context of HIV disease and for early detection of recurrent cancer or secondary malignancies in both domestic and international settings.

Clinical Evaluation of Therapeutic and Prevention Strategies

- Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., KSHV/HHV-8, EBV, HPV, and HBV) in their pathogenesis.
- Continue to support studies on the efficacy of HPV vaccines to prevent and treat cervical and anal cancer in HIV-infected populations.
- Evaluate novel approaches for the treatment of HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.

- Support approaches using gene- and protein-based technologies, such as tissue array and microarray, in targeting treatment of HIV-associated malignancies.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses in HIV-infected individuals with clinical benefit, including quality-of-life parameters; develop a staging system indicative of prognostic response and survival.
- Identify surrogate endpoints indicative of response to therapy and novel methods for evaluating tumor response in HIV-infected individuals, including imaging technology.
- Encourage and facilitate collaborative studies within clinical trials networks to develop mechanisms for early identification of individuals at high risk for AIDS-related malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of AIDS-related malignancies.
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.
- Encourage clinical studies of HIV-infected individuals with non-AIDS-defining malignancies in order to define the best treatment of these malignancies in HIV-infected individuals. Evaluate the impact of cancer therapy on virologic, immunologic, and tumor parameters; assess the toxicity of anticancer modalities in HIV-infected patients; and evaluate the pharmacokinetics of anticancer agents in HIV-infected patients, including a study of drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with anticancer therapy in HIV-infected patients, and study the effects of such strategies on virologic and immunologic parameters in HIV-infected individuals.
- Study the role of *in utero* and long-term exposure to ARVs on the risk of later development of tumors.
- Study populations in resource-limited settings at increased risk of AIDS-related malignancies due to endemic infectious agents (e.g., KSHV/HHV-8), EBV, and HPV-associated cervical cancer.

OBJECTIVE–I: *Immune Reconstitution Approaches*

Develop and assess therapeutic approaches that will restore, sustain, and enhance a competent immune system in HIV-infected individuals in domestic and international settings.

STRATEGIES

- Employ approaches to enhance immune restoration in clinical trials; test specific hypotheses of HIV immunopathogenesis.
- Evaluate the capacity of the immune system to maintain or repair itself after maximal effective viral suppression, considering the effects of gender, race/ethnicity, and age.
- Evaluate immune-based therapies for the purpose of improving ARV-sparing regimens, permitting delay in initiating or reinitiating ART.
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults, adolescents, and children, including assays that may be used in resource-limited settings.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, combinations of broad-based neutralizing monoclonal antibodies, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop and evaluate active and passive immunotherapeutic approaches (including therapeutic vaccine candidates) for HIV infection and its sequelae, including the testing of optimum immunogens; determine optimal patient disease status for response, most effective immunization dose and schedule, and most meaningful readout of clinical impact of the intervention.
- Support research on approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular immune elements, including use of expanded and/or modified peripheral blood T cells, bone marrow, cord blood stem cell transplantation, and thymic transplantation.
- Evaluate the immune system after partial restoration by effective ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents including the use of vaccines for specific OIs and coinfections.
- Develop new therapeutic strategies based on gene delivery strategies to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, and stromal cell elements from destruction by HIV.

- Evaluate the potential to inhibit HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels. Develop agents to block the attachment of HIV to receptors and coreceptors and thus inhibit entry into cells.
- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies.
- Identify immunological predictors of *in vivo* immune control of viral replication.

OBJECTIVE–J: *Treatment of HIV-Associated Complications*

Develop and assess novel interventions (e.g., complementary and alternative medicine) for the prevention and treatment of HIV disease including those prevalent in or unique to international settings.

STRATEGIES

- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other complications of HIV disease.
- Evaluate the safety and efficacy of nonpharmacologic and complementary and alternative medicine approaches, such as exercise, nutrition, and sleep cycles, in the management of HIV disease and its complications.
- Evaluate the benefits or risks of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with ART.
- Determine the role of traditional healers and the impact of the use of traditional medicines, herbal medicines, and supplements on HIV treatment and care.

CHAPTER 4

Research Support and Dissemination

Training, Infrastructure, and Capacity Building

Information Dissemination

Training, Infrastructure, and Capacity Building

AREA OF EMPHASIS

Training, Infrastructure, and Capacity Building

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Research Training*

Provide training domestically and internationally in biomedical, social, and behavioral research on HIV, with an emphasis on multidisciplinary research in racially and culturally diverse settings domestically, and with attention to the needs of marginalized communities domestically and in developing countries with high incidence and/or high prevalence of HIV infection.

STRATEGIES

- Increase predoctoral, doctoral, postdoctoral, and advanced research training across a broad range of AIDS-related disciplines.
- Support multidisciplinary training and mentoring programs to strengthen HIV/AIDS intervention research including behavioral interventions, vaccines, microbicides, therapeutics, coinfections such as tuberculosis (TB), sexually transmitted diseases, interventions to interrupt mother-to-child transmission (MTCT), nutritional interventions, and substance abuse prevention and treatment, all in the context of HIV infection.
- Expand the NIH AIDS Loan Repayment Program to increase the number of U.S. scientists and physicians from disadvantaged backgrounds, including racial and ethnic minorities, to come to the NIH to boost the cadre of trained HIV/AIDS researchers.
- Expand programs for HIV/AIDS research to develop culturally appropriate and relevant training and mentoring models to be applied to HIV-affected minority communities.
- Develop and implement programs at domestic institutions, with attention to institutions serving women and individuals from disadvantaged backgrounds, including racial and ethnic minorities, to provide precollege training to attract students interested in behavioral and biomedical sciences related to HIV/AIDS research.
- Expand the pool of domestic HIV/AIDS diversity supplement awards to ensure the research capacity of underrepresented minority investigators to make them more competitive for independent funding.

- Support HIV/AIDS research planning and organizational grants targeting domestic minority institutions and minority-serving communities. Emphasis should be placed upon grants that develop academy-community partnerships.
- Enhance opportunities through all Institutes and Centers (ICs) and programs to improve mechanisms for recruiting, training, mentoring, and retaining biomedical, behavioral, and social scientists in the conduct of interdisciplinary sex and gender analyses in HIV/AIDS research.
- Provide new opportunities and programs to attract newly trained investigators and established researchers from other fields to pursue HIV/AIDS research.
- Develop funding mechanisms to foster better linkages across AIDS-related scientific disciplines, including basic, clinical, epidemiologic, statistical, social, and behavioral science.
- Expand opportunities for institutions serving specific diverse populations at risk for HIV/AIDS to develop equal and productive partnerships with U.S. majority institutions.
- Facilitate the establishment of research partnerships between minority institutions and the communities they serve by enhancing and expanding initiatives that support research in diverse communities.
- Increase training to strengthen local capacity to conduct multidisciplinary AIDS-related prevention, vaccine, and therapeutic research in developing countries and emerging democracies by scientists from these countries.
- Strengthen cultural competency training and ethical training for the conduct of HIV/AIDS prevention, vaccine, and therapeutic clinical trials in domestic and international vulnerable populations.
- Support training programs for the diagnosis, prevention, and treatment of HIV infection and/or disease in resource-poor countries.
- Support training programs for the diagnosis, prevention, and treatment of nosocomial infections control, including TB, in resource-poor countries.
- Provide support for all HIV/AIDS training materials such as CD-ROM- and Web-based training and training sessions; all training materials must be adapted for local languages.
- Provide training in Good Laboratory Practices (GLP)/Good Clinical Practices (GCP) for translational processes and in product development in both domestic and international settings conducting HIV/AIDS clinical trials or research.
- Implement new funding mechanisms to provide research training to nonphysician professionals (e.g., physician assistants and nurse practitioners) to increase the pool of HIV/AIDS minority researchers at domestic sites and at resource-poor settings.
- Develop collaborative evaluation research efforts to assess the efficacy of strategies to shift HIV care tasks from higher-intensity to lower-intensity trained individuals in resource-limited settings.

- Support the training of biomedical and behavioral scientists in both developed and developing countries in the use of advanced computer and information technologies for HIV-related research, and ensure access to appropriate tools and equipment at the end of training.
- Support veterinary residency training programs in primate medicine at National Primate Research Centers (NPRCs) or other primate facilities to help to increase the number of highly trained veterinarians who can manage the increasing needs for HIV/AIDS nonhuman primate (NHP)-dedicated colonies.
- Support the training of veterinarian scientists who contribute to the growing need for interdisciplinary-trained researchers who help to understand both the microbial/infectious disease aspects as well as the animal model side of HIV/AIDS research in NHPs.
- Develop new models of integrated training that focus on the protection of human and animal subjects enrolled in HIV/AIDS clinical trials and on ethical issues of clinical trial design and implementation of vaccine and other prevention modalities in at-risk populations, in both domestic and international settings.
- Support training programs for personnel in resource-poor-setting institutions to strengthen the administrative and financial management capacity needed to conduct HIV/AIDS-related research.
- Expand programs to increase opportunities for scientists from developing countries and emerging democracies trained through the NIH to conduct AIDS research in their home countries (e.g., reentry grants).
- Develop new funding mechanisms and expand existing grant mechanisms to link U.S. AIDS research scientists, industry partners, and relevant institutions with each other and with investigators and institutions in both developed and developing countries.
- Take advantage of existing AIDS clinical trial infrastructures to develop specific training programs in clinical trials methodology, including issues related to the design, recruitment, retention, target population dynamics, and analysis of data, domestically and internationally.
- Expand training programs on the effective use of HIV/AIDS antiretroviral drugs and prophylactic and therapeutic interventions for coinfections/opportunistic infections as well as adequate monitoring for patient safety.
- Develop training to prevent transmission of HIV and hepatitis C (HCV) in resource-poor health care facilities, including recruitment and retention of appropriate blood donors, predonation counseling of all blood donors, improvement of blood screening strategies and technologies, and appropriate use of transfusion.
- Support training opportunities for HIV prevention researchers interested in adding specific methodological skills to their research expertise (e.g., methods to conduct cost-effectiveness analyses, measurement of biologic outcomes in behavioral intervention studies, appropriate use

of behavioral and social science measures in clinical trials, ethnographic and other qualitative methods, and network analysis).

- Support the training of members of HIV/AIDS-affected communities, to strengthen their ability to be informed partners in biomedical and behavioral science research.

OBJECTIVE–B: *Infrastructure Development*

Establish and maintain the appropriate infrastructure needed to conduct HIV research domestically and internationally with emphasis on populations of high prevalence.

STRATEGIES

- Increase research infrastructure at U.S. minority-serving institutions to improve capacity to support HIV/AIDS research.
- Enhance, improve, and maintain research capacity and infrastructure in resource-poor settings with high HIV incidence, with particular emphasis on construction and operation of facilities for research on HIV prevention, including the development of vaccines and microbicides, as well as clinical trials for therapies and behavioral interventions.
- Enhance and improve the clinical trial research infrastructure for the conduct of prevention, vaccine, and therapeutics trials in domestic and foreign sites, including laboratory capacity, trained scientists and other personnel, appropriate participant cohorts, and mechanisms to address ethical issues such as the implementation of ethical committees and translated human rights documents.
- Enhance and improve research capacity and infrastructure to advance research on AIDS-associated coinfections (HCV, herpes simplex virus type 2, Kaposi's sarcoma-associated herpesvirus or human herpesvirus type 8, human papillomavirus, Epstein-Barr virus, TB, and malaria) and associated malignancies.
- Support an adequate infrastructure for producing HIV/AIDS vaccine candidates, for preventive and therapeutic vaccine trials, under Good Manufacturing Practices (GMP).
- Support and expand adequate facilities and resources as well as appropriate ethical and procedural training to conduct HIV-related research in animal models.
- Expand the production of genetically defined specific pathogen-free (SPF) NHP, with emphasis on Indian-origin rhesus macaques.
- Develop and characterize appropriate reagents for use in HIV-related research conducted in different species of macaques and also other NHPs.
- Maintain programs that enhance the current research infrastructure, particularly the trans-NIH infrastructure, such as the Centers for AIDS Research (CFARs), the Research Facilities Improvement Program, the NPRCs, and the Clinical and Translational Science Awards.
- Provide support for, and awareness of, the Biomedical Technology Resources Program for structural studies of HIV proteins and host proteins in the context of HIV infection.

- Provide for the long-term support of advanced in-country research in resource-poor settings participating in priority AIDS-related intervention research, such as methods to interrupt mother-to-child, sexual, or parenteral transmission, or trials of candidate HIV vaccines.
- Increase collaboration between community-based organizations (CBOs) and other Government-supported service providers (such as those funded through the Health Resources and Services Administration [HRSA], the U.S. Department of Veterans Affairs, and the Centers for Disease Control and Prevention [CDC]) and academic researchers, to improve the quality and capacity of HIV/AIDS research endeavors in service settings.
- Establish and support quality-controlled repositories for, and ensure access by, qualified scientists to human samples (e.g., serum, peripheral blood mononuclear cell, plasma, patient-derived cell lines, cerebrospinal fluid, semen, breast milk, lymphoid tissues, and other key patient samples) and HIV strains from clinical trials and natural history and epidemiological studies, especially in complex study settings (e.g., MTCT studies).
- Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics to establish databases that support analyses of host and viral characteristics.
- Maintain the present AIDS-related tumor registries, and ensure linkages between AIDS and cancer registries, for both domestic and international studies.
- Improve and adequately disseminate the process of requesting, prioritizing, and receiving HIV/AIDS laboratory samples, so that access is as timely and equitable as possible.
- Promote Internet connections and availability of pertinent information technology at health science centers, hospitals, outpatient clinics, CBOs, and other access points, both domestically and internationally, for HIV-related research and patient care.
- Develop statistical sampling methodologies, data collection protocols, and statistical analysis tools that are easy to use and adaptable to different settings; facilitate efficient statistical analysis and report generation and enhance standardization, when appropriate, in the context of HIV/AIDS research.
- Promote research in, and application of, medical informatics (e.g., high-performance computing) for HIV/AIDS research and clinical practice in resource-poor settings, both domestically and internationally.
- Enhance coordination and collaboration among NIH-supported investigators, other U.S. Government agencies, and other international agencies conducting HIV/AIDS research in the same developing countries.

- Develop efficient and effective systems for collecting and managing HIV/SIV (simian immunodeficiency virus)/SHIV (chimeric simian/human immunodeficiency virus) multiple-center and single-site clinical and animal model trial data; ensure timely and accurate dissemination of clinical and animal model trial information.

Information Dissemination

AREA OF EMPHASIS

Information Dissemination

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Disseminate Information to All Constituencies*

Support the effective dissemination, communication, and utilization of HIV and AIDS information to all constituent communities of the NIH, domestically and internationally.

STRATEGIES

- Rapidly disseminate new research findings, including information on the potential implications for prevention, care, and treatment of HIV-infected individuals, using existing and innovative methods.
- Promote study designs that include plans for dissemination of appropriate and relevant findings to study participants, health care practitioners, community representatives, and policymakers.
- Facilitate the development of HIV prevention and treatment guidelines based on the latest clinical research findings.
- Utilize computer and other information dissemination technology (including the Internet) to disseminate up-to-date HIV and AIDS information; information about HIV therapeutic, vaccine, microbicide, and prevention trials; and information about HIV training programs.
- Expand access to and education about current state-of-the-art treatment and patient management guidelines, including information on clinical trials, using multiple technologies such as online access and voice access (*AIDSinfo*).
- Widely disseminate information concerning specimen repositories, including existing repositories, specimens available, and relevant information concerning cohorts, contact information, and the process for obtaining access to samples.
- Collect, archive, and promote use of existing data from NIH-supported basic and applied research for secondary data analysis, including rapid development of public use data sets that can be used for secondary data analysis in NIH-supported studies, especially baseline survey and HIV/STD (sexually transmitted disease) incidence data.
- Improve current techniques and develop and evaluate new techniques for the two-way communication of information to scientific and lay audiences, particularly to hard-to-reach populations, including information about clinical trials.

- Improve outreach and support access to AIDS information resources (including computers) by community groups, health care providers, and community-based AIDS service organizations, including those serving minority communities.
- Work with community-based organizations (CBOs), nongovernment organizations (NGOs), and local agencies to develop and promote effective methods of information dissemination on treatment, prevention, and research in target populations to increase awareness and reduce stigma.
- Support dissemination of information, including to constituent communities, in culturally and linguistically appropriate ways.
- Develop and disseminate educational information to enhance understanding of HIV and basic and clinical research processes by health care providers, community-based AIDS service organizations, social service organizations, policymakers, and persons with HIV and AIDS.
- Develop and disseminate information resources about HIV prevention, vaccine, and treatment clinical trials to increase awareness about research in these areas and the importance of supporting and participating in clinical studies.
- Evaluate the effectiveness of communication efforts by appropriate means, including obtaining feedback from target audience members through such methods as usability testing of paper and computer interfaces (see www.usability.gov) and information dissemination intermediaries, such as journalists and health educators.
- Promote wide dissemination of the annual *Trans-NIH Plan for HIV-Related Research* and other HIV-related reports as they become available.
- Promote and enhance the exchange of scientific information and communication between public and private research enterprises, such as enhancing communication with the pharmaceutical industry concerning research on the development of therapeutics, vaccines, and microbicides, and working with industrial scientists to make information concerning basic science and HIV protein structures available to the general scientific community.
- Communicate and exchange information internationally on topics such as prevention and treatment, patient management guidelines, and research results that improve the care of HIV-infected individuals, including those in developing countries.
- Support the exchange of basic and applied research information at community, regional, national, and international conferences and workshops.
- Support the cross-collaborations of HIV and AIDS information providers to develop more integrated and comprehensive information dissemination approaches.
- Provide online access to presentation materials, including full text of abstracts and other information (e.g., slides, graphics, plenary presentations) from scientific meetings.

OBJECTIVE–B: *Develop New Communications Strategies*

Support research to identify existing gaps in communication approaches, identify and evaluate existing strategies, and develop and test new and innovative communication strategies that will improve access to and use of state-of-the-art HIV information by all relevant target audiences, domestically and internationally.

STRATEGIES

- Assess the information needs and resources used by various audiences, including biomedical and behavioral research communities, health care providers, service providers, persons living with HIV and their advocates, at-risk populations, scientific and lay media, and the general public.
- Identify obstacles to information dissemination and develop, test, and evaluate possible ways to overcome these obstacles.
- Develop, test, and evaluate innovative strategies for effectively reaching specific audiences (e.g., minority communities, adolescents, drug users, other hard-to-reach populations, and health care providers) with relevant HIV information.
- Investigate how and under what circumstances different communication and dissemination strategies influence the adoption of scientifically based HIV behavior-change interventions and clinical practices in specific audiences.
- Promote use of new technologies and evaluate their effectiveness for disseminating basic and clinical research findings.
- Work to reduce communication gaps between academic researchers and treatment providers so that research results are more effectively disseminated to providers and that research agendas reflect the needs of practicing clinicians.

OBJECTIVE–C: *Coordination and Collaboration Efforts*

Develop, implement, and evaluate methods of coordination and collaboration on HIV/AIDS communications activities among NIH Institutes and Centers (ICs) and with other Federal and non-Federal groups, and international partners.

STRATEGIES

- Build and enhance partnerships among CBOs/NGOs and basic, clinical, and behavioral researchers to encourage exchange of information and experience.
- Promote and foster information dissemination regarding research and programmatic efforts across the ICs, among U.S. Government agencies, and with international partners.
- Promote collaboration among all ICs in providing information about their HIV/AIDS clinical trials to AIDSinfo and ClinicalTrials.gov.
- Expand the development of HIV/AIDS resources on the Internet to facilitate national and international research collaboration and data sharing.
- Continue collaborations with the Joint United Nations Programme on HIV/AIDS, the Pan American Health Organization, and other international AIDS agencies or societies on information/communications efforts, including information about international clinical trials.
- Collaborate with public and health sciences libraries, health care providers, AIDS Education and Training Centers, and community-based HIV/AIDS service organizations to facilitate access to needed information.
- Expand collaboration to include academic, medical, and other communities, as appropriate, in the dissemination of NIH HIV-related reports.

CHAPTER 5

Research Related to Specific Populations

Women and Girls

Racial and Ethnic Populations

Research in International Settings

Women and Girls

AREA OF EMPHASIS

Women and Girls

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Determinants of HIV Transmission*

Elucidate biologic determinants of HIV transmission and define the mechanisms by which viral, host, and immune factors may influence the process of HIV transmission, acquisition, and resistance to infection among women and girls across the life cycle. Study how or whether these determinants differ from those in men.

STRATEGIES

- Evaluate HIV transmission and acquisition in relation to viral factors, such as genotype, phenotype (inclusive of drug resistance), clade, viral load, replicative forms, viral fitness, and heterogeneity.
- Identify and characterize cells responsible for viral acquisition and propagation at mucosal surfaces in the oral cavity and the entire reproductive tract (fallopian tubes, uterus, cervix, vagina, and vulva) and anal canal.
- Evaluate HIV transmission and acquisition in relation to viral shedding in different mucosal compartments (including semen, cervicovaginal secretions, and saliva).
- Evaluate HIV transmission, acquisition, and resistance to infection in relation to age, timing, and occurrence of endocrine status changes (premenarche, menarche, postmenarche, pregnancy, premenopause, menopause, and postmenopause); the exogenous use of hormones for contraception, ovulation induction, and hormone replacement should be included.
- Over all age ranges, evaluate HIV transmission and acquisition in relation to normal vaginal (and oral) microflora and various infectious factors, such as sexually transmitted infections (STIs) and preexisting local/systemic infections with other microbes.
- Evaluate HIV transmission and acquisition in relation to host genetic factors that influence susceptibility and resistance to infection.
- Elucidate mechanisms of innate immunity and other cellular factors affecting acquisition of and resistance to HIV infection.
- Evaluate HIV transmission, acquisition, and resistance to infection in relation to other host factors, such as nutrition, nonhormonal contraception use, anatomic/physiologic changes

(female circumcision, cervical ectopy, and postdysplasia treatment), and localized inflammation secondary to use of intrauterine devices, local vaginal therapies, douches, or vaginal astringents.

- Study the biology of the systemic and mucosal immune system (innate and adaptive) in women and girls and the impact of HIV infection.
- Define how genetic, infectious, and endocrine factors alter local and systemic immune responses and the impact on HIV acquisition, transmission, and resistance to infection.
- Study the impact of effective antiretroviral therapies (ARTs) on genital tract viral dynamics (including the development of resistance) and vertical and sexual HIV transmission.

To facilitate the research goals listed above:

- Develop standardized assays for immune response and viral load, as well as other relevant parameters, in genital tract and oral samples;
- Develop noninvasive procedures for genital tract sampling; and
- Promote studies in animal models to explain host-viral-immune factors involved in HIV transmission, acquisition, and resistance to infection.

OBJECTIVE–B: *Biomedical Prevention Interventions*

Conduct and support basic and intervention research to develop, test, and evaluate safe and effective technologies and products, including vaccines and chemical and physical barrier methods that are appropriate, acceptable, and accessible to women and girls, for preventing transmission and acquisition of HIV.

STRATEGIES

- Support the discovery, development, and preclinical evaluation of new, improved, acceptable, effective, and safe chemical and physical barrier methods, including topical microbicides and other methods, to reduce sexual transmission of HIV and STIs among women and girls.
- Support the evaluation of existing chemical and physical barriers to reduce sexual transmission of HIV and STIs among women and girls.
- Support the evaluation of the contraceptive efficacy of chemical and physical barrier methods and how the efficacy affects acceptability for use in HIV prevention.
- Identify populations of women and girls with HIV incidence levels suitable for recruitment into vaccine, microbicide, and other HIV prevention intervention trials.
- Develop and evaluate methods to access, recruit, and retain women and girls who are demographically representative of the populations at risk for HIV infection for preventive intervention studies (women and girls to include racial/ethnic minorities, adolescents, substance users, and the mentally ill).
- Develop and assess the effectiveness of utilizing multiple prevention approaches, including biologic, behavioral, and community-level strategies both individually and in combination, that may decrease HIV transmission among women and girls.
- Develop and evaluate biomedical and behavioral interventions for managing STIs (including mass treatment or syndromic approaches) as a potential means of preventing HIV transmission and acquisition.
- Investigate candidate vaccines and other biomedical prevention strategies both in human subjects and in animal models of HIV infection with attention to factors particularly relevant to use in women and girls, such as changes in vaginal/cervical epithelium during puberty, pregnancy, and menopause, hormonal changes during pregnancy and menopause, the use of contraceptives or hormonal replacement therapy, and the presence of selected STIs.
- Study potential effects of candidate vaccine or microbicidal products on the genital tract immune system and mucosal integrity, and the ability of these agents to induce inflammatory activity that might compromise the integrity of the mucosal surface of the genital tract and decrease or enhance the inductive ability of vaccines and the efficacy of microbicides.

- Study the impact of biomedical interventions to prevent mother-to-child transmission, including caesarean section, on maternal morbidity and mortality.
- Support research to improve translation and dissemination and increase adoption of effective HIV prevention technologies by communities and by health care and prevention service providers who serve women and girls.
- Develop and evaluate innovative ways to obtain culturally and age-appropriate fully informed consent for participation in HIV prevention trials, and document critical aspects of informed consent (e.g., procedures, risks, benefits, voluntary nature, confidentiality, etc.).
- Study the impact of prevention interventions directed at males on the prevention of HIV and STIs in females.
- Support research to identify barriers to enrolling girls under 18 years of age in HIV prevention trials and to develop strategies for overcoming these barriers, including hard-to-reach populations such as girls living outside of family care, girls involved in the juvenile justice system, and substance abusers.

OBJECTIVE–C: *Behavioral Interventions*

Conduct and support basic and intervention research to address the female-specific, psychological, behavioral, social, environmental, economic, and cultural dynamics that increase or decrease risk for, and protection from, HIV transmission, acquisition, and disease progression among women and girls across the life cycle.

STRATEGIES

- Examine the impact of population-level interventions on HIV acquisition and resistance to infection among women and girls, such as social normative behavior changes, programs to increase educational opportunities and economic independence, mass or syndromic approaches to STI detection and control, early diagnosis and treatment of HIV infection and other STIs, use of family planning programs to diagnose and treat STIs, and availability of and access to substance abuse treatment.

- Support research across the life cycle that explores the impact of HIV risk perception on sexual activity decisionmaking, including decisions about pregnancy.

- Study how HIV-related risk and protective behaviors might change over time as a function of developmental and life-course events, such as adolescence, childbearing, sexual partnership choice and change, HIV treatment, menopause, and loss of family, social, and economic support.

- Support female-focused intervention research to prevent HIV acquisition through enhanced healthy sexual development and development of protective behaviors across the life course.

- Develop, implement, and evaluate biologic and behavioral interventions that address partnership issues regarding increased and decreased risk of HIV infection (e.g., dating, relationship violence, power in relationships, drug use, and economic survival sex).

- Develop innovative prevention strategies targeting male partners whose behaviors confer risk of HIV transmission to female partners, particularly in populations/areas with elevated HIV prevalence.

- Develop, implement, and evaluate culturally focused outreach and peer-based HIV prevention interventions that address risk behaviors and related perceptions of risk.

- Develop, implement, and evaluate prevention interventions for populations perceived to be at low risk for HIV infection, such as sexually active middle-aged and older women, college students, those with physical and mental disabilities, bisexual women and girls, women and girls residing in rural areas, Asian/Pacific Islanders, Native Americans, and Alaska Natives.

- Develop, implement, and evaluate culturally focused HIV prevention, treatment, and care interventions targeting populations of women and girls at risk due to vulnerable and/or isolating circumstances (e.g., orphaned, incarcerated, refugees, sexual exploitation, trauma, violence, war, homelessness, runaways, gang membership, and alcohol and substance abuse).

- Support research to improve translation of effective culturally focused behavioral and social science-based HIV prevention, treatment, and care interventions to communities and health care and prevention service providers serving women and girls.
- Study the impact of macro events (e.g., natural disasters, trauma, and war) on HIV risk for women and girls nationally and internationally.
- Support HIV research focused on community-level factors (social, cultural, and gender norms and ideologies) that increase or decrease risk of HIV transmission and acquisition among women and girls.

OBJECTIVE–D: *Biology of HIV Disease*

Study the biology of HIV infection, progression to disease, and development and course of clinical manifestations associated with HIV infection, coinfections, and concomitant conditions among women and girls across the life cycle. Study how or whether sex dimorphisms in HIV infection occur.

STRATEGIES

- Elucidate the unique mechanisms mediating virus-host interactions in HIV disease progression among women and girls.
  - Evaluate HIV viral dynamics and replication in blood and at the tissue level and immune function among women and girls.
  - Determine normative values for immune parameters including total lymphocyte number, subset composition, and immune cell turnover and distribution and the impact of HIV infection on those normative values across the life cycle.
  - Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including endogenous and exogenous hormonal factors (inclusive of hormonal changes across the life cycle, the menstrual cycle, hormonal contraception, and hormonal replacement therapy), pregnancy, and autoimmune diseases.
  - Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including infectious agents such as hepatitis C virus (HCV) and STIs, reexposure to different strains of HIV including drug-resistant strains, age, intermittent therapy and monotherapy for perinatal transmission, and genetic factors.
  - Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including nutrition, biological indicators of stress, drug and alcohol use, concurrent medication use, and complementary and alternative medicine approaches, including herbal therapies and nutritional supplements.
- Develop approaches for identifying, recruiting, enrolling, and retaining recently exposed and newly HIV-infected women and girls for studies on the pathogenesis of HIV infection.
- Elucidate the unique etiologies and pathogenic mechanisms of disease manifestations in HIV-infected women and girls.
  - Investigate HIV- and therapy-associated metabolic and body composition changes that may be operative at various stages of infection and disease, to include changes in fat distribution, bone density, menstrual function, fertility and sexual function, and cardiovascular disease.
  - Conduct studies on the manifestations of gynecologic disease and the efficacy of disease treatment in HIV-infected women and girls.

- Elucidate characteristics of opportunistic infections (OIs) and coinfections in HIV-infected women and girls.
- Elucidate characteristics of HIV-related malignancies, including female-specific cancers.
- Elucidate cofactors (e.g., host genetic and environmental changes) that mediate viral diseases (human papillomavirus [HPV], Epstein-Barr virus [EBV], human herpesvirus type 8 [HHV-8], hepatitis B virus [HBV], and HCV) that are associated with cancers among women and girls with HIV infection.
- Investigate the impact of infectious comorbidities on HIV-related manifestations in women and girls, including HCV coinfection, and sexually transmitted infections such as HPV and herpes simplex virus (HSV-2), and examine the impact of autoimmune disease.
- Elucidate characteristics of neurologic and neuropsychologic manifestations (e.g., dementia and changes in cognitive function) of HIV infection/disease in women and girls, including the role of potential cofactors such as substance abuse, mental health disorders, HCV infection, syphilis, and preexisting neurological conditions.
- Investigate clinical manifestations related to HIV and HIV-related therapies in pregnant and postpartum women, including toxicity (e.g., lactic acidosis and hyperglycemia) and peripartum/postpartum morbidity in HIV-infected women undergoing vaginal or operative delivery.

- Evaluate the impact of HIV and HIV-related therapies on breastfeeding.
- Explore further the role of pharmacogenetic factors as explanations for variations in HIV disease course.

OBJECTIVE–E: *Treatment of HIV Disease*

Conduct and support research to inform the diagnosis, care, and treatment of HIV-infected women and girls across the life cycle, including clinical studies of therapeutic interventions, in order to define optimal treatment strategies for females.

STRATEGIES

- Evaluate innovative and rapid testing strategies in a range of settings to identify HIV infection in women and girls.
- Assess novel case-finding approaches, including social- and risk-network-based strategies to identify undiagnosed HIV infection among women and girls and to identify women at risk for HIV infection.
- Study the psychosocial consequences of receiving HIV-positive results on women across the lifespan, including during adolescence, during the reproductive years, and during menopausal and postmenopausal stages of life, and the impact on treatment and care decisionmaking and reproductive decisionmaking.
- Evaluate the impact of antepartum and intrapartum HIV treatment on the natural history of disease and development of viral resistance.
- Enhance efforts to evaluate the efficacy and effectiveness of new and existing therapies and therapeutic regimens across the life cycle, in both treatment-naive and treatment-experienced women and girls.
- Study factors affecting adherence to HIV therapeutic regimens across the lifespan, and develop and evaluate focused interventions designed to improve adherence to HIV therapy.
- Evaluate the impact of non-HIV therapies and concomitant diseases, including substance abuse and mental disorders, on women's eligibility for participation in clinical trials, access to health care, and utilization of and adherence to treatment.
- Support research and development of clinical trial designs and statistical methodologies to evaluate clinical efficacy and reasons for success or failure of anti-HIV treatments among women and girls, including timing of treatment initiation, treatment interruptions and treatment cycling, treatment in the presence of other comorbid conditions, treatment during pregnancy, and the utility of surrogate markers.
- Conduct research to optimize diagnosis and treatment of comorbidities in women with HIV.
- Evaluate the interaction of mental health therapies and anti-HIV therapies on the course of disease progression.

- Evaluate short- and long-term toxicity, pharmacokinetics, and antiretroviral activity of therapeutic agents in women across the life cycle, including during pregnancy.
- Investigate therapeutic interactions of anti-HIV medications with other medications used by women, including interactions of ARTs with therapies for OIs; therapies for illnesses that affect women specifically, disproportionately or differently from men; hormonal treatments; treatments for substance abuse; and complementary and alternative medicine approaches.
- Evaluate the long-term effects of anti-HIV therapy on morbidity and mortality among girls and women across the life cycle.
- Measure quantity and frequency of alcohol and illicit substance use in treatment and ART pharmacology studies.
- Study the role of HPV vaccination in males and females in reducing the risk of HPV-associated cancers among women and girls with HIV.
- Elucidate the effects of ART on the occurrence of HPV-associated cancers in females.
- Conduct studies on the detection, treatment, and prevention of gynecologic disease in HIV-infected women and girls.

OBJECTIVE–F: *Consequences of HIV/AIDS*

Conduct and support basic and intervention research on the biological, psychological, social, and economic consequences of HIV/AIDS and associated stigma for infected and affected women and girls.

STRATEGIES

- Conduct multidisciplinary research to understand the synergistic effects of HIV-related disease progression and premorbid and comorbid clinical and psychosocial conditions affecting women and girls, and the mechanisms underlying these effects; develop interventions to enhance physical and mental health outcomes.
- Develop and evaluate interventions that target HIV-serodiscordant couples to prevent transmission and to promote coping and quality of life.
- Support research to understand the consequences of HIV infection and disease progression on women's and girls' sexual and reproductive health and reproductive decisionmaking. This includes research on the decision to disclose HIV status and the consequences of disclosure.
- Support research to improve understanding of reproduction intentions and sexual behaviors of women who are or whose partners are HIV-infected, and how fertility intentions are influenced by highly active antiretroviral therapy (HAART); develop and evaluate accessible assisted reproductive technologies designed to assist in meeting goals for reproduction without vertical or horizontal HIV transmission.
- Conduct research to examine the consequences of HIV infection and treatment on women's and girls' access to, receipt of, and adherence to treatment for comorbid conditions, including other infectious and noninfectious diseases, substance abuse, and psychiatric illness.
- Examine the association between gender-specific physical and psychosocial consequences of HIV disease and HIV-related treatment initiation and maintenance.
- Develop and evaluate interventions to reduce adverse psychological, social, and economic consequences for women and girls infected or affected by HIV/AIDS, such as educational and economic opportunities, access to treatment and care, and prevention of violence and abuse.
- Conduct basic research to understand the dynamics of gender-specific stigma/discrimination associated with HIV/AIDS and to inform the development of structural interventions to reduce HIV/AIDS-associated stigma.

OBJECTIVE–G: *Access to Research and Services*

Identify and address the factors that influence women's and girls' access to and experience of HIV/AIDS-related research, care, support, treatment, and prevention services.

STRATEGIES

- Support research to understand how the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care, reproductive health, family planning, and social services affect HIV risk behaviors, HIV transmission, and access to appropriate HIV care, support, treatment, and prevention services.
- Support research to develop effective strategies for the linkage, coordination, and integration of HIV care, support, treatment, and prevention services with primary medical care; drug, alcohol, and mental health treatment; STI services; cancer care, particularly cancer screening programs; reproductive health and family planning services; educational services; and community social services.
- Conduct research to examine transition of HIV/AIDS care across the lifespan, from pediatric to adolescent to adult care, and from adult to geriatric care, and develop interventions to optimize transition of care.
- Support research to understand the impact of policy and policy change—such as health care, health sector reform, health care financing systems, legislation, and regulations—on the delivery and utilization of HIV-related services, HIV risk behavior and transmission, and HIV/AIDS disease outcomes among women and girls.
- Encourage multidisciplinary research to identify unmet needs and elucidate barriers for women and girls to achieving optimal HIV care, support, treatment, and prevention services.
- Support research to study and address factors that influence the full participation of women and girls in HIV/AIDS-related research, including clinical trials for novel therapeutics and vaccines.
- Support research on effective strategies for disseminating products, findings, and information from HIV/AIDS-related research to women, girls, their communities, and policymakers.

OBJECTIVE–H: *Ethical Issues*

Conduct and support research, training, and education on ethical issues specifically affecting women and girls in HIV/AIDS-related clinical, behavioral, epidemiological, and health care services research in different cultural settings.

STRATEGIES

- Develop and evaluate efforts to educate women and girls who are potential trial participants about ethical and human rights issues in human research in advance of recruitment, with the goal of obtaining fully informed and free consent.
- Investigate the unintended consequences of policies and practices (including research practices) that provide special benefits to HIV-infected—as compared to uninfected and unaffected— women and girls (e.g., preferential treatment, health care benefits, access to medications, and social services). Conduct research to examine and determine the contexts and factors that influence when the consent process is fully voluntary and is an informed aspect of the consent process.
- Investigate unintended harms and benefits that may accrue to women and girls, their families, and their communities as a result of participation in research studies.
- Examine the ethical risks and benefits of studies that involve treatment versus observation of women and girls.
- Investigate the ethical impact within a community of studies in which clinical trials provide the only access to therapeutics for women and girls.
- Assess potential negative and beneficial consequences for women and girls of conducting community-level epidemiological research.
- Study the ethical issues related to diagnostic and therapeutic strategies during pregnancy and lactation.
- Study the ethical issues related to breastfeeding and its alternatives.
- Study the ethical issues related to participation of women and girls in clinical trials.

Racial and Ethnic Populations

AREA OF EMPHASIS

Racial and Ethnic Populations

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Determinants of Risk*

Develop and conduct population-specific primary research that focuses upon the individual, interpersonal, organizational, cultural, and community determinants of risk.

STRATEGIES

- Examine the impact of traumatic stressors upon HIV-risk behavior and HIV resiliency in indigenous domestic populations. These populations include Native Americans, Alaska Natives, Native Hawaiians, and Pacific Islanders.
- Develop studies that assess the impact of acculturative stress and historical trauma upon HIV-risk behaviors and HIV-health-seeking behavior among those disproportionately affected by the epidemic of HIV infection, including racial and ethnic populations.
- Explore the effect of poverty, residential segregation, educational opportunity disparities, incarceration, and health illiteracy upon the ongoing disparity in HIV transmission among racial and ethnic populations across the lifespan.
- Increase the emphasis on research that examines the influence of race, ethnicity, language fluency, and gender, independently and collectively, upon the social and cultural contexts of HIV acquisition, transmission, and risk.
- Stimulate research to identify what constitutes sexual behavior 'norms' in racial and ethnic populations.
- Determine the impact of gender-based violence, intimate partner violence, and a history of childhood sexual abuse upon HIV risk in racial and ethnic minority populations, including transgenders.
- Promote primary research on the determinants of HIV risk, including substance abuse, in racial and ethnic minority transgendered individuals, social networks, and underlying health disparities.
- Stimulate research on the impact of social and sexual networks upon HIV resiliency and risk.

- Design and conduct studies that determine the impact of stigma, racism, and racial/cultural stereotyping in promoting or impeding early and sustained access to HIV prevention, care, and treatment.
- Stimulate research that explores the influence of bias, racial and cultural prejudice, and homophobia upon health care providers, health care systems, and HIV-testing behaviors among the racial and ethnic populations they serve.
- Explore the effects of hormonal replacement and its biological impact upon racial and ethnic minority transgenders and HIV risk.
- Study the biological (including genetic), environmental, and physiological factors that affect HIV acquisition, transmission, and progression within racial and ethnic populations.
- Explore the behavioral, biological, cultural, and social factors that affect HIV risk, acquisition, and transmission in older women, especially women of color.
- Stimulate exploratory research upon the impact of migration upon HIV-risk behavior, comorbid sexually transmitted infections, and disease burden within racial and ethnic populations.
- Recruit and retain racial and ethnic minorities in numbers sufficient to provide adequate statistical power to detect racial and gender differences in NIH-sponsored studies, especially Phase III clinical trials.
- Explore the impact of adolescent and youth culture upon adolescent HIV-risk behaviors, especially among racial and ethnic populations, to determine how this affects them, their social peer networks, and their risk of HIV acquisition.
- Study the social networks of youth of color and the impact the age of a partner has upon their HIV risk and the risks to those within their respective sexual networks.

OBJECTIVE–B: *Intervention Research*

Develop population-specific, theory-based interventions that focus upon individual risk, community norms, organizational and sociocultural factors, as well as biological susceptibility.

STRATEGIES

- Identify effective interventions for racial and ethnic minority communities, as well as for those in sexual minority within those communities, that prevent HIV acquisition and transmission.
- Recruit and retain racial and ethnic minorities in numbers sufficient to provide adequate statistical power to detect racial and gender differences in NIH-sponsored studies.
- Explore processes of engagement that make for effective community prevention responses.
- Study the social aspect of prevention delivery from the role of key informants to key community organizations, and the linkages necessary for community acceptance of prevention.
- Identify the factors that reliably predict and assess the level of community readiness to engage with HIV prevention or other research interventions.
- Fund community-academic partnerships that have demonstrated linkages with community-based organizations to promote the development of effective and accepted community prevention interventions.
- Develop, pilot, and test new models of HIV behavioral interventions that incorporate common stressors and experiences for racial and ethnic minorities, including acculturation, racism, and stigmatization.
- Identify structural and behavioral factors that affect HIV testing and testing frequency among racial and ethnic populations.
- Determine what venues are perceived as acceptable and accessible for HIV testing by racial and ethnic populations.
- Encourage the development, piloting, and testing of prevention efforts for high-risk uninfected individuals within health care systems for non-HIV-related conditions.
- Identify successful interventions to increase access to and quality of care in racial and ethnic communities, and their subsequent impact upon HIV transmission in these communities.
- Develop interventions that document the impact of evidence-based quality of care and best practices upon HIV disease outcome in racial and ethnic populations.

- Explore social marketing and health communication strategies used by the private sector to develop new effective HIV prevention interventions in racial and ethnic minority populations.
- Identify effective, efficient, and sustainable HIV prevention interventions for rural communities, especially those with undocumented immigrants.
- Develop, pilot, and test HIV prevention interventions for efficient and rapid translation into the field.
- Develop, pilot, and test new models of HIV behavioral interventions that incorporate common resilience factors for racial and ethnic populations, including cultural identity, spirituality, and collectivism.

OBJECTIVE–C: *Methodology*

Develop and test innovative methods and measures to accurately assess determinants of risk, including resiliency and social norms in populations at highest risk for HIV infection.

STRATEGIES

- Develop, pilot, test, and evaluate new measures of HIV-risk behavior that are culturally and contextually appropriate for racial, ethnic, and sexual minority populations.
- Develop and test new sampling methodologies for populations most heavily affected by HIV infection.
- Develop and standardize assessment tools that are designed for the at-risk community in which they are to be used, including rural populations, foreign-born individuals, and racial and ethnic populations.
- Develop novel sampling methods to enhance the proportion of underrepresented populations that continue to be disproportionately affected by HIV infection in clinical and prevention research, such as racial and ethnic minorities, adolescents, the homeless, and indigenous populations.
- Emphasize the development of intervention evaluation methods that can translate results quickly from the field to the communities affected.
- Evaluate models for HIV prevention, care, and treatment with HIV-infected individuals in heavily affected communities utilizing comprehensive, culturally and contextually appropriate interventions.
- Develop, pilot, and test effective models for increasing the awareness of the benefits of HIV testing in racial and ethnic minority populations.
- Develop models to include community-initiated HIV prevention interventions and evaluation in community-academic partnerships, especially in disproportionately affected communities.
- Incorporate community-based participatory research principles into all community-based projects to ensure the bidirectional benefit and investment of the community and the research team.
- Identify the components of effective outreach, and develop models of successful outreach with quantification of that success.
- Identify factors that increase HIV risk among racial and ethnic minority transgendered individuals; develop, pilot, and test models of HIV prevention that modify those risks.

OBJECTIVE–D: *Factors Affecting Risk*

Support high-risk, high-impact research that explores the unique factors that affect HIV-risk behavior, acquisition, transmission, and resistance for those at highest risk for HIV infection within racial and ethnic minority communities.

STRATEGIES

- Explore the interface between countries, their borders, and the impact of these borders on HIV-risk behavior within the racial and ethnic populations along those borders.
- Stimulate public-private-academic collaborations that study the unique factors that affect HIV-risk behavior in racial and ethnic populations and develop interventions based upon these unique factors.
- Identify the impact of the provision of stable housing upon HIV-risk behavior, disease outcome, and treatment adherence.
- Determine the impact of insurance payor status on care-seeking behavior, treatment adherence, and remaining in care.
- Explore the relationship between employment type (e.g., day labor versus part-time) upon HIV-risk behavior in heavily affected communities, including racial and ethnic populations.
- Stimulate multidisciplinary research that links risk management (e.g., substance abuse treatment) and HIV-risk reduction through novel cross-DHHS (U.S. Department of Health and Human Services) agency partnerships and joint funding.
- Determine the impact of educational initiatives upon health literacy and the downstream impact upon HIV-risk awareness and behavior.
- Fund collaborative, multidisciplinary partnerships that target core sociocultural factors in HIV transmission and explore the impact upon HIV-risk behavior and transmission.

Research in International Settings

AREA OF EMPHASIS

Research in International Settings

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: *Capacity Building*

Develop a sustainable, collaborative research environment by utilizing and enhancing in-country capacity.

(The scientific objectives of A and B are of equal weight and serve as a prerequisite foundation for objectives C through I.)

STRATEGIES

Site Development

- Encourage the integration of NIH-supported research programs being conducted in resource-limited countries by U.S. researchers with established in-country programs, including collaboration with local investigators on strategic planning for research.
- Assess existing sites and, as needed, further develop sustainable, existing in-country sites, or establish new international research sites as rapidly as possible to address urgent and emerging scientific opportunities.
- Enhance capacity for the conduct of basic and applied prevention and treatment research, with emphasis on maintaining and developing both Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) requirements for large-scale clinical trials, through:
  - strengthening laboratory capacity through the provision of required equipment and human resource development, with appropriate quality assurance and training;
  - developing clinical capabilities through research training and "hands-on" research experiences;
  - developing affordable alternatives to viral load and CD4+ cell counts and expensive laboratory monitoring for treatment efficacy and toxicity;
  - supporting the analysis of scientific and research-based international databases and developing common laboratory information management systems;
  - enhancing data collection and analysis capabilities;
  - addressing barriers in maintaining, optimizing the use of, and ensuring human subject protections related to repositories of biological samples in resource-constrained countries;

  - developing and testing strategies for recruitment and retention of participants in prevention, treatment, and care studies;
  - enhancing the ability to ensure protection for human subjects involved in research and the ethical conduct of research, including informed consent and issues specific to women and children and vulnerable populations, including injection drug users (IDUs), men who have sex with men (MSM), prisoners, and sex workers;
  - enhancing mechanisms for information exchange among investigators, including enhanced electronic communication;
  - conducting research on rapid and sustainable scale-up from pilot projects and/or early Phase I and II trials to large research studies, including Phase III trials, and on how to apply and implement research findings to the general population;
  - strengthening community advisory boards to participate in the development and design of clinical trials and other research, as well as in the translation of research results into programs and policies;
  - strengthening financial management, accounting, and business office practices; and
  - strengthening library services and access to scientific resources.
- Build global capacity to conduct operational research, including outcome and cost-effectiveness studies and modeling, to rapidly address emerging priorities in prevention, treatment, and care.
- Conduct studies on incidence and feasibility, using appropriate incidence measures (e.g., population-specific assays), in order to identify sites suitable for the conduct of efficacy trials of HIV prevention, treatment, and care interventions.
- Develop and provide training at international sites conducting vaccine studies on the role and responsibilities of an institutional biosafety committee (IBC).
- Develop regional approaches to research (e.g., through regional meetings and training) to enhance communication and to address common issues and needs among countries in a region.

Collaboration and Coordination

- Ensure that foreign investigators are full and equal partners with U.S. scientists in the design, conduct, and analyses of clinical studies.
- Enhance coordination of NIH international AIDS research, particularly when multiple projects are active in the same country and/or region.
- Encourage the continued development of research collaborations between international and U.S. investigators, ensuring project relevance to strategic planning at the local level, to maximize the

research effort in resource-limited settings; and encourage U.S. researchers to participate at the developing country research site to better understand the challenges of conducting research and providing care and services in such settings.

- Provide assistance to foreign collaborators in addressing regulatory issues and special oversight mechanisms.
- Coordinate with other U.S. Government agencies, including the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), the Department of Defense (DoD), the Health Resources and Services Administration (HRSA), and the State Department (e.g., the Office of the Global AIDS Coordinator [OGAC] and the President's Emergency Plan for AIDS Relief [PEPFAR]).
- Work with foreign governments, international organizations (e.g., the World Health Organization [WHO]), the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM), nongovernmental organizations (NGOs), private industry, foundations, and alliances (e.g., the Global HIV Vaccine Enterprise) to help identify priorities, gain efficiencies, and reduce overlap in the development and testing of vaccines, microbicides, drugs, and other prevention, care, and treatment strategies, including behavioral interventions.
- Explore collaborations with reputable indigenous health providers and nonphysician health research professionals (e.g., nurses, pharmacists, etc.) to better understand their roles and practices in AIDS care and prevention; to facilitate their involvement as partners and indigenous health professionals in global AIDS research, care, and prevention; and to identify practices that may add value in treating and preventing diseases in diverse geographical settings.

Ethical Issues

- Ensure that research projects are designed to benefit the countries in which the research is being conducted.
- Enhance the capability of institutions in resource-limited settings to conduct independent scientific and ethical reviews, while ensuring timeliness of the review process.
- Ensure education/cross-fertilization between resource-limited countries' ethical review committees and U.S. institutional review boards (IRBs), and educate U.S. IRBs about cultural issues in developing countries.
- Ensure the participation of local researchers/scientists, communities, NGOs, governments, indigenous leadership of vulnerable populations, and other stakeholders in the development of research protocols.
- Ensure that ethical challenges in both research and the implementation of research results in resource-limited settings are clearly described and addressed in grant proposals.

- Ensure confidentiality of information about HIV-infected individuals, including information on individuals in treatment for substance abuse.
- Ensure that ethical review mechanisms, such as informed consent forms, are relevant and appropriate to the country where the research is conducted and are placed in cultural context.
- Conduct workshops on ethical principles and their implementation in research, encouraging countries to develop their own set of ethical guidelines and procedures, to include the principles of respect for persons, beneficence, and justice, and the application of informed consent, assessment of risks and benefits, and selection of subjects.
- Encourage in-country scientists and leaders to work closely with local journalists to foster understanding of science, the role of research, and relevant ethical issues.
- Conduct research designed to identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings, including a focus on informed consent.

Technology Transfer and Translation of Research Results

- Ensure results are provided to and understood by participants and staff involved in research studies and available for their use.
- Develop distance learning approaches to enhance communication of research results and translation into prevention, treatment, and care programs.
- Provide improved access to information concerning treatment and prevention guidelines and the results of research through enhanced information technology.
- Facilitate development of locally appropriate and acceptable HIV prevention and treatment guidelines, by including behavioral, basic, epidemiological, and clinical research findings.
- Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptom management, clinical training, and patient care programs once research studies are completed.
- Support operational research based on implementation science and innovative research designs not limited to randomized clinical trials (RCTs).

OBJECTIVE–B: *Mentoring and Training Investigators*

Develop an in-country community of investigators committed to a culture of leadership in research through providing sustainable mentoring for junior investigators and career development opportunities for new, mid-career, and senior investigators.

(The scientific objectives of A and B are of equal weight and serve as a prerequisite foundation for objectives C through I.)

STRATEGIES

- Ensure the leadership role of in-country investigators and influential individuals in countries where studies take place by involving them 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 and law enforcement officials.

- Provide sustainable career development opportunities for new, mid-career, and senior investigators (e.g., similar to long-term career awards and institutional grants offered domestically) in resource-limited international settings.

- Develop in-country training partnerships, and support "south-to-south" training to enable investigators to obtain training appropriate for the areas in which they will work by (1) developing a cadre of in-country scientific professionals, and (2) providing opportunities to enable trained investigators returning to their home countries to serve as training resources for others.

- Continue to support research training, both in-country and in the United States, of clinicians (physicians and nonphysician professionals, e.g., nurses, midwives, pharmacists, etc.), public health professionals and community health workers, and scientists from developing nations to enhance the conduct of research on HIV, AIDS, sexually transmitted infections (STIs), and other HIV-related coinfections, malignancies, and comorbidities, including research training related to (1) biomedical, social, and behavioral prevention research, (2) prevention of mother-to-child transmission (MTCT), (3) treatment and care, (4) clinical trials of therapeutic strategies, (5) development and testing of vaccine candidates, (6) impact of alcohol and other substance abuse/dependence on HIV transmission, treatment, and disease outcome, (7) reproductive health, including microbicides, and (8) disease progression.

- Provide training in data collection, management, and analysis for in-country research personnel.

- Provide training to enable in-country researchers to meet the requirements of GCP and GLP, including training and maintenance of medical records.

- Provide training in the ethical conduct of research, including informed consent, establishment of community advisory boards, and other topics related to the protection of human subjects.

- Provide training in all aspects of grantsmanship, including preparation of grant proposals, registration for electronic submission, grants management, reporting requirements, research administration, and fiscal accounting.
- Provide training to ensure that clinicians and other health care workers are knowledgeable about infection control principles and can implement proper procedures in resource-constrained countries.
- Enhance training in translational, operational, and health services research.

OBJECTIVE–C: *Structural Interventions*

Conduct studies to identify effective structural and policy interventions to address the AIDS epidemic.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Determine barriers and facilitators to acceptance of voluntary counseling and testing (VCT), and develop more comprehensive and integrated health system-level approaches to the provision of VCT, including:
  - assess new VCT approaches for cost-effectiveness and impact on reducing risk from sexual behavior and drug use in settings with varying levels of HIV seroprevalence;
  - integrate VCT into other existing health services, including family planning; and
  - change community norms for seeking VCT that encourage knowledge of one's status, help mitigate social harm, and reduce HIV stigma.
- Identify the most effective and sustainable ways for schools, leisure locations, and worksites to support behavior change interventions.
- Investigate the effectiveness of community-based and community-level HIV prevention programs, including prevention education and strategies to evaluate, replicate, and extend effective behavioral interventions.
- Investigate the structural and policy-related human rights limitations that affect HIV prevention, treatment, and care for vulnerable populations (e.g., MSM, prisoners, IDUs, and sex workers), including laws and policies related to discrimination against minorities engaged in same-sex behavior between consenting adults, and evaluate the effectiveness of rights-based interventions to improve HIV disease outcomes.
- Ensure that all research is conducted in culturally appropriate content, form, and format.
- Ensure that all research is conducted in accordance with international standards of human rights principles and in accord with the dignity of persons.
- Evaluate the effectiveness of expanded access to drug abuse and treatment programs, including sterile injection equipment and syringe exchange programs, and the policy-level changes necessary to implement such expanded interventions.
- Develop and test strategies for encouraging voluntary partner notification within the context of families and couples counseling.
- Evaluate the effectiveness of expanded access to male circumcision programs and the policy-level changes necessary to implement such expanded interventions.

OBJECTIVE–D: *Interventions to Alleviate Stigma and Discrimination*

Support AIDS research to develop interventions that address the issues of sex/gender, age, power relationships, stigma, and discrimination.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Conduct research on sex/gender and age differences and/or inequities in access to and use of resources, information, and prevention and care services, as well as adherence issues.
- Conduct research on the impact of new technologies and structural interventions (e.g., male circumcision) on gender and power relationships.
- Encourage analysis of sex/gender and age differences in all relevant HIV-related research.
- Study gender-related social and behavioral factors affecting acquisition of HIV infection, including intimate partner violence and the conflicting demands of childbearing and avoidance of disease.
- Study gender-related biological factors affecting susceptibility to HIV infection, including the use of contraception and the presence of sex-specific conditions, such as human papillomavirus (HPV) infection and cervical cancer.
- Study age-related social, behavioral, and biological factors (including the use of medications) affecting susceptibility to HIV infection and its transmission.
- Study the psychological impact of HIV infection in women, including their role as heads of households and/or caregivers, the impact of additional pregnancies, and family support.
- Develop interventions to mitigate the negative social consequences of HIV infection related to AIDS stigma and discrimination, with particular emphasis on children infected with or affected by HIV (e.g., AIDS orphans).
- Evaluate laws and legal policies at the local, State, and national levels that operate to sustain stigma.
- Design and evaluate strategies to reduce stigma and discrimination and increase willingness of individuals to enter into voluntary counseling and testing; identify, accept, and implement alternative infant feeding practices; and receive and adhere to antiretroviral therapy (ART) and antituberculosis drug regimens.
- Support training of community and public health leaders to become role models in the implementation of such strategies and interventions.

OBJECTIVE–E: *Prevention of Risk Behaviors in Social Settings and Networks*

Study the significance of interactions among individuals in groups engaging in various risk behaviors, and develop and evaluate interventions and strategies to prevent HIV-risk behaviors in social settings and high-risk networks.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Develop sustainable behavioral and community-specific interventions to address multiple risk factors.
- Conduct research to integrate the multiple components of diverse issues of sexuality, alcohol and other substance use, and mental health into HIV prevention programs.
- Develop and test prevention strategies that address relationships between noninjection drug use and sexual transmission.
- Develop interventions targeted to both HIV-infected and HIV-uninfected individuals that are designed to appeal to specific populations such as women, men, adolescents, and the military.
- Develop and test prevention interventions to be used in the family context to prevent risky behavior and HIV acquisition and transmission by its members.
- Study the role of migration in the spread of the HIV epidemic in diverse geographical regions.
- Identify the most effective means to reach and prevent HIV transmission among mobile populations, including migrants, refugees, and those displaced by national conflict or natural disaster.
- Support cross-border studies to study virus transmission issues as well as the impact of various policies and structural interventions related to migration and immigration.
- Conduct studies to develop interventions at multiple levels (e.g., individual, couple, group, and society) that reflect and address regional aspects of the epidemic.
- Investigate the role of mental health conditions (e.g., depression) and alcohol and other commonly used psychoactive substances in promoting or facilitating high-risk sexual behaviors that reduce the efficacy of prevention strategies.
- Define sexual and drug use behaviors and their predictors in HIV-infected populations, and design and test interventions to reduce the risk of HIV transmission.
- Determine the factors involved in high-risk social networks (e.g., injection and noninjection drug users and heavy drinkers and/or alcohol-dependent individuals) that influence the rates and patterns of HIV infection, and design prevention programs based on these results.

- Encourage molecular epidemiology studies of viral diversity in the context of social networks.
- Study how alcohol use, including systems of payment using alcohol, affects increases in HIV risk in seasonal and nonseasonal migrant populations.
- Conduct studies to identify sustainable interventions at the levels of the individual, social network, community, and society to prevent HIV and hepatitis C virus (HCV) transmission as a result of high-risk sexual activity and/or drug use practices.
- Devise strategies to prevent initiation of drug use, alcohol dependence, and transition to riskier drug practices, such as initiating drug injection and sharing of injection equipment.

OBJECTIVE–F: *Biomedical Prevention Interventions*

Develop and evaluate biomedical prevention interventions and strategies.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Evaluate techniques for detection of acute HIV infection, and study the effects of early identification of potential HIV transmitters on HIV infection spread in different settings.
- Utilize population-based studies to examine basic scientific questions about HIV infection, mechanisms of transmission, and host responses, including viral evolution, viral diversity, human immunology, and mucosal factors in transmission.
- Study the risk of transmission of drug-resistant strains of HIV.
- Develop and evaluate methods for increasing access to, acceptability of, and adherence to biomedical interventions.
- Study and integrate the behavioral aspects of biomedical interventions and strategies.

Male Circumcision

- Determine the durability of effectiveness of circumcision in reducing HIV transmission risk in men.
- Study the effect of male circumcision on HIV transmission risk from men to women and from men to men.
- Develop and evaluate innovative strategies for the safe and effective delivery of male circumcision and other male-oriented prevention services to prevent or reduce HIV transmission.
- Determine the factors affecting male circumcision use and acceptance.
- Study the sociocultural aspects that may inhibit or encourage use of circumcision.
- Study the technical training and implementation requirements for widespread uptake of circumcision interventions.
- Determine the cost-effectiveness of male circumcision in limiting transmission and curtailing the expansion of the epidemic.

Antiretroviral Use

- Determine the effectiveness of pre- and postexposure antiretroviral (ARV) prophylaxis in prevention of sexual and blood-borne HIV transmission.
- Determine the most effective ARV agents or combinations of agents to reduce transmission risk.
- If proven effective, determine the social, cultural, and practical factors affecting ARV use and/or providing barriers to implementation of exposure prophylaxis.

Vaccine Development

- Continue the accelerated efforts toward development of vaccine candidates suitable for use around the world, and foster the development of vaccines to optimize characteristics appropriate for broad international use, including candidates exhibiting low cost with ease of production and administration, as well as stability.
- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects.
- Provide a scientific knowledge base (incidence, viral subtypes, major histocompatibility [MHC] types, and natural history) to guide decisionmaking regarding the need for clinical trials in international sites and to conduct trials in these sites and communities according to the highest clinical and ethical standards.
- Identify suitable populations of adults and children to enroll in clinical trials of candidate vaccines, while ensuring equitable and appropriately representative gender balance in enrollment.
- Conduct Phase I, Phase II, and Phase III clinical trials for safety, immunogenicity, and efficacy, with appropriate surrogate markers and measures of correlates of protection with suitable candidate vaccines in domestic and international settings.
- Enlist the participation of local community representatives in the development of appropriate trial protocols, as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively address the social and medical concerns of the participants; and establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale of the study.
- Examine relevant behavioral issues related to the conduct of vaccine research and its acceptability in diverse populations.
- Conduct research on the social and economic impact of vaccines and their cost-effectiveness.

Microbicides and Barrier Methods

- Discover and develop candidate microbicides and other physical/chemical barrier methods to prevent sexual HIV transmission.
- Conduct Phase I, Phase II, and Phase III clinical trials for safety and efficacy with suitable candidate microbicides in domestic and international settings.
- Develop appropriate biological and surrogate markers of safety or protection.
- Determine the efficacy and use of prevention interventions, including microbicides and other physical/chemical barrier methods, and determine the factors affecting their use and acceptance.
- Study the sociocultural aspects that may inhibit or encourage microbicide use and barriers to adherence.
- Study the sociocultural and behavioral concerns related to partner involvement and acceptance of microbicide use or covert use in the absence of partner willingness or acceptance.
- If found to be effective in preventing HIV transmission/acquisition, determine the cost-effectiveness of microbicides and other physical/chemical barrier methods in limiting transmission and curtailing the expansion of the epidemic.

STIs and Other Diseases

- Determine the efficacy and cost-effectiveness of syndromic management of STIs among HIV-infected individuals to prevent HIV transmission.
- Improve clinical management of viral STIs in HIV-infected individuals, emphasizing coinfections with herpes simplex virus (HSV)-2 and HPV.
- Identify gender-related biological factors affecting susceptibility to HIV infection, including the use of hormonal contraceptives and the presence of gender-specific conditions such as HPV infection, cervical cancer, and genital ulcer disease.
- Examine the impact of coinfection with other endemic diseases on HIV disease, including the risk of acquiring and/or transmitting HIV infection and disease progression.
- Determine the role of sexual transmission of HCV in coinfection with HIV.

Substance Abuse

- Develop and evaluate innovative, culturally relevant, contextually appropriate alcohol and drug abuse treatment programs for their utility as HIV and HCV prevention approaches in different international settings.
- Develop and evaluate approaches for drug and alcohol abuse programs among HIV- and HCV-coinfected patients to improve adherence with drug/alcohol treatment strategies.
- Develop and evaluate innovative strategies for identifying "hidden populations" of young, older, and out-of-treatment drug users.

MTCT: Considerations for the Mother, Child, and Family

- Develop and evaluate strategies for primary prevention, i.e., prevention of HIV acquisition by adolescent girls and women.
- Investigate methods to improve reproductive health in serodiscordant couples, including HIV-risk reduction in *in vitro* fertilization.
- Develop and evaluate strategies for prevention of unwanted pregnancy by HIV-infected adolescent girls and women.
- Investigate the mechanisms of and risk factors for *in utero*, intrapartum, and postnatal MTCT by HIV-infected adolescent girls and women.
- Investigate the unique immune status of pregnant women and their infants and develop immune interventions to interrupt HIV transmission.
- Facilitate and develop targeted prophylactic drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Further evaluate and adapt known efficacious interventions in infants, mothers, or both to prevent MTCT (antiretroviral prophylaxis, cesarean section before labor and before ruptured membranes, complete avoidance of breastfeeding, exclusive breastfeeding).
- Develop effective, safe, and feasible strategies for prevention of MTCT of HIV, using interventions that are affordable and can be implemented in resource-constrained settings, especially with regard to prevention of MTCT through breast milk.
- Study factors associated with unwanted repeat pregnancies in HIV-infected women.
- Evaluate strategies to reduce the morbidity and mortality associated with MTCT of HIV, including:
  - the role of maternal and infant nutrition during the peripartum and postpartum periods;

  - the impact of the health status of HIV-infected mothers on the survivability of both HIV-infected and HIV-uninfected children; and
  - short- and long-term toxicity of ARVs used for prevention of MTCT in women during pregnancy and in their offspring who were perinatally exposed.
- Evaluate and reduce the maternal and pediatric morbidity associated with mode of delivery.
- Develop strategies to reduce the risk of postpartum morbidity (e.g., endometritis, hemorrhage, pneumonia) related to cesarean section for prevention of MTCT of HIV.
- Develop strategies to reduce the risk of iatrogenic preterm birth and associated respiratory morbidity.
- Evaluate mechanisms to reduce the maternal and pediatric morbidity and mortality associated with infant feeding modality, including the role of exclusive breastfeeding and acceptability of safe breastfeeding alternatives.
- Evaluate the development of antiretroviral resistance, clinical outcomes among HIV-infected women and their children, and impact on subsequent pregnancies according to receipt of/exposure to antiretrovirals (*in utero*, intrapartum, and postpartum/postnatal).
- Quantify more precisely the risk of MTCT when maternal HIV infection is acquired during pregnancy, including:
  - the effectiveness of known efficacious interventions to prevent MTCT; and
  - development of strategies for detecting or reducing maternal incident infection during pregnancy.
- Evaluate strategies and identify the obstacles and facilitators for scaling up successful interventions for prevention of MTCT of HIV.

OBJECTIVE–G: *Treatment Research*

Develop and evaluate the most effective, setting-specific strategies for care and treatment of HIV and HIV-related conditions and their sequelae among HIV-infected and HIV-affected children, adolescents, and adults at all stages of the life course.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Determine affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment.
- Evaluate and monitor treatment efficacy, adherence, side effects, drug-drug interactions, and toxicity of ARVs and prophylaxis medications against major coinfections in pediatric, adolescent, and adult (including over age 50) populations in resource-constrained settings.
- Collaborate with clinicians from resource-limited countries to recruit and retain acute and early HIV infection cases in treatment research programs.
- Determine the role of pharmacogenetics/pharmacokinetics and identify appropriate ARVs that can be used in specific populations (e.g., children, adolescents, and adults at all life stages) in resource-constrained countries.
- Determine the efficacy of ARV regimens on various clades prevalent around the world.
- Investigate interactions of ARVs with alcohol, drugs of abuse, or medications used for the treatment of substance abuse.
- Develop, evaluate, and implement programs to prevent discrimination in the provision of ARV treatment.
- Characterize the clinical course of HIV infection in diverse geographic settings.
- Identify conditions that emerge as a consequence of ART and longer survival, such as malignancies, neurological and neuropsychological conditions, and metabolic and nutritional dysfunctions.
- Support the long-term followup of children exposed to ART *in utero* and/or postpartum to evaluate possible late effects of ARV exposure.
- Assess the impact of nutritional status and nutritional interventions on patient survival and the efficacy and tolerability of ART, including measuring the rate of immune system deterioration.
- Develop and evaluate public health models, such as family and community models of care for infants to older adults that integrate HIV/AIDS care and other existing health services in a single setting to maximize outcomes and avoid duplication of effort.

- Enhance interdependent programs such as programs for tuberculosis (TB) control and management of other comorbid conditions, alcohol and other substance abuse/dependence treatment programs, maternal and child health services, and support services for the elderly.
- Develop and evaluate strategies to initiate and provide care to targeted groups of individuals such as health care workers, security forces, and teachers.
- Conduct community-based studies that assess the impact of community mobilization on treatment success.
- Examine the effectiveness of a variety of approaches to the administration of therapy (e.g., directly observed therapy or directly delivered therapy).
- Conduct studies, including clinical trials and operational research, on the quality of treatment, its effectiveness, and its efficacy.
- Develop and test strategies, including promotion of treatment literacy, to support adherence in adults of all ages, adolescents, and children to medication regimens to enhance therapeutic outcomes and limit the development of drug resistance.
- Investigate the impact of alcohol abuse, drug abuse, and other associated comorbid conditions on HIV disease progression, adherence to treatment regimens, and clinical outcomes.
- Conduct research on biological, behavioral, and psychosocial effects related to the natural history and care of HIV disease among children and adolescents.
- Develop and evaluate suitable and sustainable approaches to the diagnosis of HIV infection, especially for children under the age of 18 months.
- Develop and evaluate suitable and sustainable approaches to monitoring the effectiveness and safety of HIV treatment, especially with regard to affordable technologies to measure CD4+ cell counts and viral load (or appropriate alternatives).
- Assess the cost-effectiveness of ARVs in resource-limited settings and determine the minimal level and methods of targeted drug resistance monitoring necessary in those failing therapy and in pregnant women.

OBJECTIVE–H: *Endemic Diseases and HIV*

Study the interactions between HIV infection, comorbidities, and endemic diseases, with a particular focus on endemic diseases that affect HIV care and are a part of the spectrum of HIV comorbidities, and develop strategies to optimize their integrated prevention, diagnosis, treatment, and care.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Examine the role of coinfection and other endemic diseases and their treatment in modulating HIV infection or disease, including risk of acquiring and/or transmitting HIV infection, disease progression, and the use of ART.
- Determine the impact of ART on susceptibility to infection with endemic diseases, and on their natural history.
- Determine the impact of ART on the efficacy of treatment and prophylaxis for other endemic diseases.
- Investigate drug-drug interactions of ARVs and drugs used to prevent and treat endemic infections and/or other manifestations of such endemic infections.
- Define the spectrum, incidence, and risk factors for HIV-related sequelae (e.g., coinfections such as TB, HCV, and HPV, malignancies, and organ system-specific manifestations such as renal disease, eye disease, and urologic, neurological, and neuropsychiatric conditions) in adult, adolescent, and pediatric populations specific to individual regions in diverse geographic settings.
- Determine optimal ways of integrating treatment for HIV disease with prevention of and treatment for opportunistic infections (OIs), endemic diseases, and comorbidities, especially TB, including clinical research to assess clinical outcome and operational research to determine cost-effectiveness.
- Develop, study, and widely and uniformly deploy new, low-cost, and rapid diagnostic and drug susceptibility tests for comorbid and endemic diseases (including TB) and new agents and therapeutic strategies to treat drug-sensitive and drug-resistant TB (including multi-drug-resistant [MDR]-TB and extensively drug-resistant [XDR]-TB).
- Develop and study strategies for primary and secondary TB prevention, including prophylactic regimens.
- Develop and study feasible and effective strategies for prevention of transmission of drug-susceptible and -resistant TB in community and health care settings.

- Assess the impact of available antibiotic treatment and prophylaxis regimens to optimize therapeutic approaches for TB and other endemic coinfections in the context of ART, including new therapies for TB and new approaches to administering drugs.
- Determine the safest and most efficient treatment modalities for endemic diseases (e.g., TB, HCV, HIV-associated cancers, and malaria) in the adult, pediatric, and adolescent populations infected with HIV.
- Assess the burden of TB and the relative importance of reactivation versus *de novo* infection in HIV-coinfected individuals in various settings.
- Develop methods to monitor development of antimicrobial resistance by HIV-related and endemic pathogens infecting both study participants and the general population.
- Investigate behavioral and cultural factors related to endemic coinfections, within the context of HIV disease, and develop strategies to enhance and monitor adherence to therapy and prophylaxis for endemic coinfections in HIV-infected individuals.
- Investigate sustainable strategies for preventing, treating, and monitoring response to treatment of endemic diseases in HIV-infected adults, adolescents, children, and infants in resource-constrained settings.
- Determine the safety and effectiveness of available immunizations for endemic pathogens in diverse HIV-infected populations.
- Develop simple clinical algorithms for guiding initiation of prevention or treatment of HIV-related OIs and comorbidities.
- Identify affordable strategies to target high-risk patients for initiation of prophylaxis for HIV-related OIs and comorbidities.
- Conduct studies to better understand the role and mechanism of reinfection and/or superinfection with HCV in coinfected individuals.

OBJECTIVE–I: *Impact of Prevention and Treatment*

Evaluate the impact of prevention and treatment programs on the HIV epidemic, integrating comprehensive prevention and clinical care in existing health service delivery programs related to HIV/AIDS, while leveraging clinical trial sites for prevention interventions.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Assess the social, psychological, societal, and economic impact of ART on risk behaviors, HIV transmission, and prevalence, including associated behavior change, in individuals (including children), families, and various communities.
- Determine the impact of ART availability on utilization of VCT in various communities.
- Determine the impact of ART availability on entry into care and treatment.
- Determine whether expanded ART care and treatment leads to a decrease in HIV-associated stigma and discrimination.
- Determine effective strategies for integrating the delivery of HIV care with drug treatment, alcohol treatment, TB treatment, and other medical and social services commonly needed by HIV-infected individuals.
- Evaluate the impact of interactions between HIV therapeutics, alcohol, drug abuse, or medications used for the treatment of substance abuse on the maintenance of anti-addiction therapy and on MTCT.
- Determine the impact of ART on breastfeeding behaviors.
- Identify morbidities in HIV-exposed, uninfected infants and young children, using appropriate control populations, in resource-constrained settings.
- Study the direct effects of ART on HIV transmission, e.g., by evaluating the effectiveness of specific ART strategies in curtailing HIV transmission in HIV-serodiscordant couples.
- Determine the public health impact of ART, specifically the likelihood of transmission of drug-resistant virus and the natural history of disease in people infected with a drug-resistant HIV strain.
- Examine the potential use of HIV therapeutic vaccines.
- Determine the impact of ART on the development of drug-resistant strains of HIV in diverse geographical settings, and develop strategies to limit its development. Develop biomarkers that can serve as surrogates for measurement of HIV-risk behavior and can be used to predict and monitor rapid escalation of HIV subepidemics.

- Integrate operational and health services research with clinical research to facilitate the translation of research findings to clinical practice and public health programs and to provide information to inform the scale-up of HIV prevention, care, and treatment programs.
  - Develop strategies to ensure that prevention efforts in resource-limited countries are simultaneously preserved and enhanced when treatment clinical trials and, later, ART treatment programs are established, and when prevention trials are completed.
  - Conduct research on how best to deliver prevention education in the care and treatment setting, targeting interventions to both HIV-uninfected and -infected individuals.
  - Develop culturally appropriate mechanisms to identify persons for whom treatment is indicated and to overcome factors such as stigma and discrimination, which can forestall testing and limit the provision of treatment and care.
  - Develop links with other agencies and organizations to integrate research with service programs and to develop multidisciplinary prevention research in multiple settings, including medical treatment and community support and care organizations.
  - Develop strategies to control the HIV epidemic that address multiple health outcomes simultaneously without compromising existing public health infrastructure, while at the same time strengthening infrastructure to improve health outcomes.
  - Evaluate the impact of scale-up of HIV prevention, care, and treatment programs on the health system as a whole and its ability to deliver other public health services, particularly in resource-limited settings.

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Appendices

NIH Institutes and Centers
List of Acronyms

APPENDIX A:

NIH Institutes and Centers

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CIT	Center for Information Technology
CSR	Center for Scientific Review
FIC	John E. Fogarty International Center
NCCAM	National Center for Complementary and Alternative Medicine
NCMHD	National Center on Minority Health and Health Disparities
NCRR	National Center for Research Resources
CC	NIH Clinical Center

APPENDIX B:

List of Acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
CAB	community advisory board
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CFARs	Centers for AIDS Research
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
DC	dendritic cell
DoD	U.S. Department of Defense
DHHS	U.S. Department of Health and Human Services
EBV/HHV-4	Epstein-Barr virus
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HAART	highly active antiretroviral therapy
HAD	HIV-associated dementia
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HHV-4/EBV	Epstein-Barr virus
HHV-8/KSHV	herpesvirus type 8
HIV	human immunodeficiency virus

HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HSV-2	herpes simplex virus type 2
IBC	institutional biosafety committee
ICs	Institutes and Centers
IDU	injection drug user
IRB	institutional review board
KS	Kaposi's sarcoma
KSHV/HHV-8	Kaposi's sarcoma herpesvirus
MCMD	minor cognitive and motor disorders
MDR-TB	multi-drug-resistant TB
MHC	major histocompatibility complex
MRSA	methicillin-resistant *Staphylococcus aureus*
MSM	men who have sex with men
MTCT	mother-to-child transmission
NGO	nongovernment organization
NHP	nonhuman primate
NIH	National Institutes of Health
NPRC	National Primate Research Center
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OI	opportunistic infection
PDA	personal data assistant
PrEP	preexposure oral chemoprophylaxis
SHIV	chimeric simian/human immunodeficiency virus
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	sexually transmitted infection
TB	tuberculosis
TOC	test of concept

UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
USMHRP	U.S. Military HIV Research Program
VCT	voluntary counseling and testing
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB

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