Overview

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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.