Overview

Overview

"Like a pebble dropped in a pool, HIV sends ripples to the edges of society, affecting first the family, then the community, then the nation as a whole. By targeting predominantly young and middle-aged adults who are the mainstay of the economy and the principal support of their families, the epidemic destroys the very fabric of societies. Particularly in places where HIV prevalence is high, it hamstrings economic growth and makes the provision of social services more difficult. And in a vicious twist, by exacerbating poverty it makes populations more vulnerable to the spread of AIDS." UNAIDS

THE GLOBAL HIV/AIDS PANDEMIC

According to the June 2007 Report of the Global HIV Prevention Working Group, "The global HIV/AIDS pandemic continues largely unabated. If current trends continue, it is projected that 60 million more HIV infections will occur by 2015, and the annual number of new HIV infections will increase by 20 percent or more by 2012." The AIDS pandemic will continue to wreak devastating consequences around the world for decades to come for virtually every sector of society. The pandemic affects the future of families, communities, military preparedness, national security, political stability, national economic growth, agriculture, business, health care, child development, and education in countries around the globe. The United Nations General Assembly's Declaration of Commitment on HIV/AIDS states: "...the global HIV/AIDS epidemic, through its devastating scale and impact, constitutes a global emergency and one of the most formidable challenges to human life and dignity, as well as to the effective enjoyment of human rights, which undermines social and economic development throughout the world and affects all levels of society…."

AIDS AROUND THE WORLD

As of the end of 2007

- Approximately 33.2 million people worldwide are living with HIV/AIDS.
- Approximately 2.5 million are children under the age of 15 years.
- About half of the infected adults are women.
- An estimated 2.5 million people (adults and children) acquired HIV in 2007.
- The global HIV/AIDS epidemic killed approximately 2.1 million people in 2007.
- More than 25 million people have died since the beginning of the epidemic.

Source: UNAIDS/WHO 2007 AIDS Epidemic Update

THE EPIDEMIC IN THE UNITED STATES

More than 25 years into the epidemic, AIDS continues to be a major public health problem in the United States with more than 40,000 estimated new infections annually. Despite enhanced prevention interventions and advanced HIV treatment regimens, HIV/AIDS continues to be a formidable public health challenge that disproportionately affects communities of color, men who have sex with men, women of color, and persons age 50 and over. HIV surveillance data provide a more complete picture of the epidemic than AIDS cases alone, given that the time to progression from HIV infection to AIDS can be 10 or more years. Although the number of estimated HIV cases declined among certain age groups, the number of HIV/AIDS cases increased among those ages 15–64, with the largest number occurring among persons 35–39 years of age. Similarly, HIV/AIDS cases continue to increase among women of color, men who have sex with men, and adolescents. The rate of AIDS diagnoses for black adults and adolescents was 10 times the rate for whites and nearly 3 times the rate for Hispanics. The rate of AIDS diagnoses for black women was nearly 23 times the rate for white women. The second highest rate of AIDS diagnoses was for Hispanics/Latinos, followed by Native Americans and Alaska Natives.

Advances in treatment have increased the life expectancy and improved the quality of life for individuals living with HIV; however, these treatments are associated with a number of side effects and long-term complications that may ultimately have a negative impact upon HIV/AIDS-associated morbidity and mortality. In addition to the side effects of HIV treatment, numerous coinfections are associated with or are exacerbated by immune deficiency, including but not limited to tuberculosis, hepatitis B, and hepatitis C. An increase in the number of individuals with HIV-TB coinfection, as well as an increase in the number of drug-resistant TB cases, have been reported by CDC. In addition, HIV is associated with a number of comorbidities, including malignancies, cardiovascular disease, neurological disease, and autoimmune conditions. 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

- 952,629 cumulative AIDS diagnoses through 2005
- 530,756 cumulative AIDS deaths through 2005
- Approximately 1.1 million Americans living with HIV infection; 25 percent unaware of their infection
- Approximately 40,000 new infections annually, unchanged in more than 10 years

Source: CDC HIV/AIDS Surveillance Report, June 2007

THE NIH AIDS RESEARCH PROGRAM

The NIH has made the largest and most significant public investment in AIDS research in the world. Its response to the epidemic requires a unique and complex multi-Institute, multidisciplinary, global 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. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of the NIH Institutes and Centers (ICs).

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. This is recognized in the unique role given the Office of AIDS Research (OAR) in its authorizing legislation, the NIH Revitalization Act of 1993. That law establishes OAR as a model for trans-NIH coordination, vesting it with primary responsibility for overseeing all NIH AIDS-related research. It is the unique role of OAR, part of the Office of the Director, 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. OAR is enhancing trans-NIH collaboration, minimizing duplication, and ensuring that research dollars are invested in the highest priority areas of scientific opportunity that will lead to new tools in the fight against AIDS. As such, OAR represents the roadmap for NIH AIDS research, allowing the NIH to pursue a united research front against the pandemic.

THE OAR TRANS-NIH PLANNING AND BUDGET DEVELOPMENT PROCESS

As mandated by law, the Director, OAR, in collaboration with the ICs, non-Government experts from academia, foundations, and industry, and community representatives, develops the annual *Trans-NIH Plan for HIV-Related Research*. The Plan shapes NIH investments in biomedical and behavioral AIDS research and provides the framework to translate critical research findings to benefit populations desperately in need both in our country and abroad. Based on the most compelling scientific priorities that will lead to better therapies and prevention strategies for HIV infection and AIDS, the Plan serves several important purposes:

- As the framework for developing the trans-NIH AIDS research budget.
- For determining the use of NIH AIDS-designated dollars and for tracking and monitoring those expenditures. The Plan thus defines those research areas for which AIDS-designated funds may be allowed.
- As a document that provides information to the public, the scientific community, Congress, and AIDS-affected communities about the NIH AIDS research agenda. OAR distributes the annual comprehensive Plan to a wide audience, and it appears on the OAR Web site: http://www.nih.gov/od/oar.

OAR has established a unique and effective process to build consensus around the scientific agenda established by this strategic plan. OAR has established trans-NIH Coordinating Committees, chaired by senior OAR scientific staff, for each of the major scientific and crosscutting Areas of Emphasis of the Plan, which are National History and Epidemiology; Etiology and Pathogenesis; Microbicides; Vaccines; Behavioral and Social Science; Therapeutics; Training, Infrastructure, and Capacity Building; Information Dissemination; Women and Girls; Racial and Ethnic Minorities; and Research in International Settings. These Committees, comprising representatives of the ICs with major research portfolios in the corresponding Area of Emphasis, provide an ongoing mechanism for collaboration, coordination, and information exchange.

To develop the FY 2009 Plan, the Coordinating Committees prepared the first draft by reviewing and updating the FY 2008 Plan, considering the state of the science and recent progress in their Areas of Emphasis. They identified emerging scientific opportunities and knowledge gaps and revised and reprioritized the Scientific Objectives for each Area of Emphasis as appropriate. In addition, they eliminated those Strategies where research is no longer a high priority and added new Strategies to address questions revealed by recent scientific discoveries and newly emerging public health needs. In this way, the planning process serves to monitor and assess scientific progress on an annual basis.

Once the draft FY 2009 Plan was developed, OAR sponsored a series of planning workshops to seek input of non-NIH experts from academia, foundations, industry, and the community in each of the Areas of Emphasis. These experts worked with the NIH Coordinating Committees to further refine and amend the Plan and reach consensus on key scientific priorities. Participants in each Planning Group were asked to review and revise the draft Objectives and Strategies of the Plan based on the state of the science, and to identify a set of priorities for their Area of Emphasis. All groups were asked to address needs in Information Dissemination and in Training, Infrastructure, and Capacity Building, as related to their scientific areas.

The resulting draft Plan then was provided to each IC Director and designated IC AIDS Coordinator for additional review and comment from the IC perspective. Finally, the draft Plan was reviewed by the Office of AIDS Research Advisory Council (OARAC). A list of all of the members of the Planning Groups can be found at the end of this document.

TRANS-NIH AIDS RESEARCH PORTFOLIO ANALYSIS

OAR continues to reassess and refine the AIDS research planning process to better capture the broadest range of scientific expertise and to identify the highest scientific priorities. In FY 2006, a critical new element was added to the annual process—a multitiered comprehensive trans-NIH review of all grants and contracts supported with AIDS-designated funds. This highly successful review established a new model to ensure that AIDS research dollars support the highest priority science, taking into account the ever-changing domestic and international AIDS epidemic, as well as the evolving scientific priorities. This process now has been implemented as an integral component of the annual OAR strategic planning and budget processes. This portfolio analysis allows OAR to

direct the transfer of funds to better manage the AIDS research portfolio and assist OAR in developing the trans-NIH AIDS research budget from the commitment base.

Each of the OAR staff who chairs a scientific Coordinating Committee initiates a review of each NIH extramural project within their scientific area supported with AIDS dollars, concentrating on those eligible for recompetition in the fiscal year of the strategic Plan. Working with relevant IC program staff, OAR staff identify projects that are currently of lower priority scientifically than when they originally were funded. This does not mean that these grants should not have been funded or were not of high priority at the time they were funded. However, as the science has progressed, and the priorities for addressing the epidemic have shifted, these scientific areas may no longer represent the highest priorities articulated in the Plan for the current budget. For example, many grants were awarded to address basic research on pathogens that cause opportunistic infections. Over the past few years, with the advent of combination antiretroviral therapy, the infections caused by these pathogens are no longer common among HIV-infected individuals; therefore, basic research on the pathogens that cause coinfections now is deemed of lower priority for AIDS-designated funding. The determination of "low priority for AIDS funding" is not related to the scientific or technical merit of the projects, but only to their relevance within the current AIDS research agenda as it relates to the changing demographics of the epidemic, scientific advances, and new opportunities.

After review of the grant portfolio by NIH and IC program staff, OAR convenes a meeting of a small group of eminent non-Governmental scientists to provide their expert advice; review each scientific area and all of the grants identified as low priority; and provide recommendations for redirecting funds to catalyze future initiatives and multidisciplinary endeavors. OAR notifies each IC of those grants identified as too low a priority for support with AIDS dollars. Each IC has an opportunity to reinvest those dollars in priority AIDS programs in their portfolio. For those ICs that cannot identify higher priority projects, those dollars are shifted to other ICs with higher AIDS research priorities needing additional support. Should the investigator choose to submit a renewal application that is determined to be highly scientifically meritorious in the peer review process, the IC may choose to fund the project with non-AIDS dollars.

TRANS-NIH COMPREHENSIVE AIDS RESEARCH BUDGET

The law provides that OAR shall allocate all appropriated AIDS research funds to the Institutes and Centers according to the *Trans-NIH Plan for HIV-Related Research*. The Plan provides the framework for the annual budget development and allocation process. Based on the priorities and objectives established in the Plan, the ICs submit their AIDS-related research budget requests to OAR, focusing on new or expanded program initiatives for each scientific area. 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 total amount to allocate for AIDS research within the overall NIH budget, as required by law. Within that total, OAR allocates the AIDS research budget levels to 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 absorb and expend resources for 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, those dollars are coded to the appropriate objective(s) of the Plan and reported to the OAR AIDS Research Information System, a trans-NIH database of all AIDS-related expenditures, including extramural, intramural, and research management and support.

STRUCTURE OF THE PLAN

The Areas of Emphasis of the Plan are grouped into five functional chapters—Foundational Research, Prevention Research, Therapeutics Research, Research Support and Dissemination, and Research Related to Specific Populations—to more clearly define the relationship among them and their function within the overall research agenda. Each Area of Emphasis of the Plan includes a comprehensive list of Scientific Objectives, in priority order, that address the many needs and challenges within the field of HIV/AIDS research. As mentioned above, all NIH expenditures with AIDS-designated funds are coded and tracked to these Objectives. Included with each Objective is a set of Strategies that provides examples of approaches that might be taken to fulfill each Objective. To underscore the interrelationships among areas, some Strategies may be found under more than one Area of Emphasis.

THE PLAN IS ORGANIZED AS FOLLOWS:

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 within the Plan.

- **Natural History and Epidemiology:** Since the beginning of the HIV epidemic, 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 being affected, requires rigorous epidemiologic studies be conducted in different settings, both domestically and internationally. 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. 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. Tremendous progress has been made in understanding the fundamental steps in the life cycle of HIV, the host-virus relationship, and the clinical manifestations associated with HIV infection and AIDS. Groundbreaking research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, methodologies for diagnosis, and monitoring of the safety and effectiveness of antiviral therapies. The results of this research are the basic building blocks for the development of new drugs, vaccines, microbicides, and prevention strategies. Continued support for basic research is a critical element in the fight against HIV/AIDS.

CHAPTER 2, PREVENTION RESEARCH: Prevention Research includes basic, translational, and clinical research on microbicides and vaccines development, and behavioral and social sciences associated with HIV transmission, acquisition, and care. There is an urgent need to expand the range of interventions for preventing HIV transmission beyond those currently available.

- **Microbicides:** Microbicides, defined as antimicrobial products that can be applied topically for the prevention of sexually transmitted infections, including HIV, may offer one of the most promising primary preventive interventions that could be safe, effective, readily available, affordable, and widely acceptable. Microbicides used alone or in combination with other prevention strategies could be used both by HIV-infected individuals to prevent transmission to their partners and by uninfected individuals to protect themselves from acquiring HIV. The NIH supports a comprehensive microbicide research program that includes the screening, discovery, development, preclinical testing, and clinical evaluation of compounds with the potential to act as antimicrobial agents with both spermicidal and nonspermicidal activity. In addition, the NIH supports behavioral and social science research on the acceptability and use of microbicides among different 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. As a result of increased NIH-supported vaccine research, many new approaches are being pursued and several vaccine candidates are in the pipeline. Moreover, the NIH supports research to identify and better understand protective immune responses. Information gleaned from these studies is being used to inform the design and development of novel vaccine strategies. As promising candidates move further in the vaccine pipeline and through initial clinical testing, expanded trials with populations at increased risk for HIV infection will become increasingly important. Therefore, the NIH continues to actively support research-related capacity building in regions that have a high prevalence of HIV/AIDS, both domestically and internationally.

- **Behavioral and Social Science:** The NIH supports research to better understand how to influence the behaviors that lead to HIV transmission—including preventing their initiation—and how

to maintain protective behaviors once they are adopted in all populations at risk. The NIH sponsors research related to: developing, implementing, and evaluating behavioral and social science interventions to 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. Many of the methodologies of behavioral and social science are applicable to both prevention research and research on care and ameliorating 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 minority communities, will contribute to the successful implementation of a broader range of preventive and/or therapeutic strategies.

CHAPTER 3, THERAPEUTICS RESEARCH: NIH-supported AIDS therapeutics research has led to the development of therapeutic regimens that have extended the length and quality of life for many HIV-infected individuals in the United States, Western Europe, and elsewhere where antiretroviral drugs are available. The use of antiretroviral therapy continues to result in improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities associated with antiretroviral drugs. However, the global impact and continued spread of the AIDS pandemic in both developed and developing nations underscore the importance of the development of therapeutic regimens that can be implemented in international settings. The NIH supports a comprehensive AIDS therapeutics research portfolio that includes discovery, preclinical development, and clinical testing of new drugs and multidrug therapeutic regimens, including postlicensure comparison studies. In addition, the NIH supports research aimed at combating HIV-related coinfections and comorbidities, such as tuberculosis, hepatitis C, malignancies, metabolic disorders, cardiovascular disease, and neurologic disorders, which are becoming increasingly prevalent as HIV-infected individuals live longer. Antiretroviral drugs also have been used successfully to prevent mother-to-child transmission. NIH-supported studies are underway that are exploring the preexposure uses of antiretroviral therapy to prevent HIV infection. Additional research is needed to develop improved therapeutic strategies that will extend the treatment success that has been realized in the United States to resource-limited settings.

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

- **Training, Infrastructure, and Capacity Building:** Because of the global nature of the HIV pandemic, the NIH supports training of domestic and international biomedical and behavioral AIDS researchers, as well as the improvement of facilities and equipment for the conduct of AIDS-related research and clinical studies. The expansion of NIH-funded AIDS research glob-

ally has necessitated the development of research infrastructure in many locations, including resource-limited settings in Africa, the Caribbean, India, and Asia. Numerous NIH-funded programs have increased the number of training positions for AIDS-related research, including programs specifically designed to recruit individuals from underrepresented populations into research careers and to build research infrastructure at minority-serving institutions. Additionally, the NIH Loan Repayment Program (LRP), mandated by Congress in Public Law 100-607 in 1988, has attracted many health professionals to the NIH to engage in AIDS-related research.

- **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 groups 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, both domestically and internationally. (Funding for the areas in this final Chapter is not tracked by Objective.)

- **Women and Girls:** Women experience HIV/AIDS differently from men, both physiologically and socially. While basic mechanisms of viral replication and pathogenesis may not differ significantly in women and men, research has shown that there are sex or gender differences in the way HIV interacts with its host through the course of HIV disease. NIH-sponsored researchers are studying the ways in 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 might play a role in transmission, acquisition, 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 and immune responses in the reproductive tract, and cofactors, such as coincident infections with other sexually transmitted disease pathogens.

- **Racial and Ethnic Populations:** HIV infection, like many other disease states, reflects the ongoing health disparities among racial and ethnic populations in the United States. Prevalence of HIV infection in these communities is disproportionately higher than in majority communities.

In many U.S. urban centers, the prevalence of HIV infection is similar to rates found in the developing world. These findings, along with the resurgence of sexually transmitted diseases that have been shown to increase the risk of HIV transmission and acquisition and associated high-risk behaviors, underscore the need for comprehensive strategies to decrease HIV transmission in affected vulnerable populations and to improve treatment options and treatment outcomes. The NIH is directing increased resources toward research to develop interventions that will have the greatest impact on these groups. These include interventions that address the cooccurrence of other sexually transmitted diseases, hepatitis, drug abuse, and mental illness, and interventions that consider the role of culture, 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 trials, as well as in natural history, epidemiologic, and prevention studies.

- **Research in International Settings:** Since the early days of the epidemic, the NIH has supported research efforts in countries affected by HIV and AIDS. Beginning in 1984, with a research project in Haiti and the establishment of Project SIDA in 1985, in what was then Zaire, the NIH has maintained a strong international AIDS research portfolio. The NIH has expanded its research effort to encompass approximately 90 countries around the world. Results of this research benefit not only the people in countries where the research is conducted, but people affected by HIV/AIDS worldwide. NIH-sponsored international research includes efforts to develop: HIV vaccine candidates; chemical and physical barrier methods, such as microbicides, to prevent sexual transmission; 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. Although industrialized nations have experienced a dramatic decrease in transmission of HIV from infected mother to her child, preventing this transmission is a significant challenge in resource-poor settings of the world; strategies that can effectively be used in such settings continue to be pursued.

Critical AIDS Research Priorities

During the development of this Plan, the Planning Groups for each Area of Emphasis of the Plan were asked to identify the most critical research priorities in their area—research deemed most worthy of additional funds if they were available. All of the suggested priorities were then presented to and considered by the senior scientific staff of OAR. In the distillation of all the suggested priorities, two clear themes emerged to focus research across all of the areas: prevention of acquisition and transmission of HIV, and prevention and treatment of HIV-associated comorbidities, comortalities, and coinfections.

These priorities, defined below, will guide the development of the FY 2009 AIDS budget and will be utilized to adjust the FY 2008 AIDS budget as needed.

Prevention of Acquisition and Transmission of HIV

The NIH will give highest priority to research that will:

Develop and test biomedical prevention technologies that apply basic knowledge of how HIV enters cells, as well as behavioral intervention strategies to prevent the establishment and spread of HIV between individuals and within communities.

- Develop further understanding of 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.
- Develop further knowledge of the biological mechanisms that govern the entry of HIV into target cells, particularly with relation to the interactions of HIV envelope and cell receptors, and apply that knowledge to develop microbicides and vaccines to prevent acquisition and to block transmission of HIV.

Continue to design, develop, and test candidates and strategies that will increase the likelihood of preventing HIV infection.

- Develop novel biomedical strategies (microbicides and vaccines), as well as practical social interventions, that can be applied to appropriate risk groups.
- Evaluate existing biomedical strategies (microbicides and vaccines) in clinical trial settings, which will explore various high-risk transmission/acquisition scenarios (e.g., acquisition from male and female sexual partners, blood-borne transmission/acquisition associated with drug use, and transmission from mothers to breastfeeding infants) to inform and optimize future product design and application.

- Identify markers or bioassays that will be predictive of efficacy and safety of biomedical interventions.
- Conduct implementation or operational research to foster the scale-up and use of existing efficacious interventions to prevent HIV infections.
- Develop and test methods of intervening at structural, environmental, and community levels to reduce transmission and acquisition of HIV. Focus attention on prevention strategies that could be implemented in racial and ethnic communities, particularly in young women, with high incidence of HIV infection and to groups, such as young men who have sex with men (MSM).

Prevention of HIV infection remains the NIH's highest priority in AIDS research. Biomedical studies and related research efforts in behavioral and social science have yielded an impressive body of knowledge related to the mechanisms of transmission and acquisition at the molecular, cellular, tissue, individual, and community levels. Despite increasing knowledge about the cellular targets and the modes of HIV transmission, the overall rate of newly acquired HIV infections in the United States has remained constant for more than a decade, though the rate among young women and MSM of racial and ethnic communities continues to increase. In resource-constrained countries and the world at large, HIV infections continue to increase at an unacceptably high rate.

There is a continuing need for basic science research to inform the development of prevention technologies that integrate biomedical and behavioral interventions. Examples of areas where increased emphasis is likely to produce insights for prevention include mucosal immunology and biology studies to determine methods to prevent entry of HIV into target cells at the mucosal interface. Importantly, 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 more controlled, 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. In addition, use of alcohol or drugs of abuse may have both behavioral and health consequences that relate to susceptibility to infection.

Ongoing test-of-concept trials of microbicides and HIV vaccine candidates should be completed as efficiently as possible so that currently available products can be evaluated for their ability to prevent acquisition and/or disease progression. It is anticipated that these test-of-concept trials will inform future product formulation as well as clinical trial design. As new candidates emerge from basic and preclinical testing, they should be expeditiously advanced through the product development pathway and into clinical trials.

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, often present a barrier to large-scale implementation. However, 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. For example, a multiple-session, small-group intervention might be practical in clinical settings or other venues where at-risk persons are concentrated, but it is not practical as a general population intervention. It is important, therefore, to determine which is the best strategy and optimal setting for different populations or social networks.

The NIH expects that a significant amount of useful information for prevention efforts will continue to be generated through studies on the mechanisms of infection and of the natural history of infection. In most infected individuals, HIV infection is marked by immune dysfunction, depletion of CD4+ T cells, impaired cytokine production, and relatively unencumbered viral reproduction. Studies of virology and immunoregulation have identified some mechanisms by which these effects are produced, but more is yet to be learned about the interdependencies and interactions of immunological control mechanisms and the virus. For example, the roles of CD25+ regulatory T cells in immunoregulation are only beginning to be understood. By studying individuals who do not develop clinical disease or who develop it only much later than normally expected, it seems likely that new avenues of preventive interventions can be developed. Similarly, an understanding of the behavioral or biological (immune or genetic) mechanisms that explain why repeated exposure to HIV does not lead to infection in certain individuals would be valuable information for vaccines and other prevention efforts, as well as treatment.

Finally, the NIH recognizes that, while HIV transmission and acquisition are fundamentally processes that occur at the individual level, there are interventions that might be applied at structural, environmental, and community levels that will affect the course of the continued spread of the HIV pandemic. Research has already identified some means to intervene at these levels. There is a continuing need to understand how HIV operates as a virus that is transmitted in the course of human relationships, occurring in social contexts that vary by location and culture. Notable examples include condom use programs among sex workers, needle exchange programs, placement or delivery of risk-reduction information in venues where risk behavior occurs, changes in policies to allow broader use of agonist therapies for drug abuse, and broader implementation of aggressive detection and treatment programs for sexually transmitted diseases associated with HIV risk. However, neither these nor individually based interventions have had sufficient impact, especially among racial and ethnic minority communities and domestic communities of MSM, for whom the Internet has proven to be an efficient means of facilitating sexual risk behavior. Given the continuing high incidence of HIV infection in these communities, interventions to reach and change the behaviors of large numbers of at-risk individuals are urgently needed. Structural and broad-scale interventions that do not necessarily require contact between an intervener and an individual recipient of an intervention (as in a counseling relationship) are needed to reach and affect large numbers of individuals. The prevention field could benefit from additional innovative studies on environmental modifications, network perturbations, policy interventions, and other broad-scale prevention methods. Studies are particularly needed to develop interventions that target MSM as well as men and women from racial and ethnic populations.

CRITICAL AIDS RESEARCH PRIORITIES

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 TB and HCV.

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 tolerate their toxicities and side effects, and can adhere to complicated treatment regimens. 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 antiretroviral therapy (ART). Basic research is needed to better understand the pathogenesis of the disease, as well as the mechanisms of toxicity of antiretroviral drugs that are resulting in these manifestations and complications. Epidemiologic studies are needed to determine the incidence and prevalence of these comorbidities in various populations, as well as to determine, monitor, and evaluate the effects of gender, race, age, pregnancy 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.

The development of optimum strategies for the prevention and treatment of HIV coinfections (including TB and HCV) 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 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 to prevent and treat HIV coinfections. Critical research will focus on the development, preclinical evaluation, and clinical testing of new agents for the treatment of TB. New treatment regimens are needed that will cause fewer side effects and drug interactions. In addition, therapies are required that will be effective against multi-drug-resistant and extensively drug-resistant TB in HIV-infected individuals.