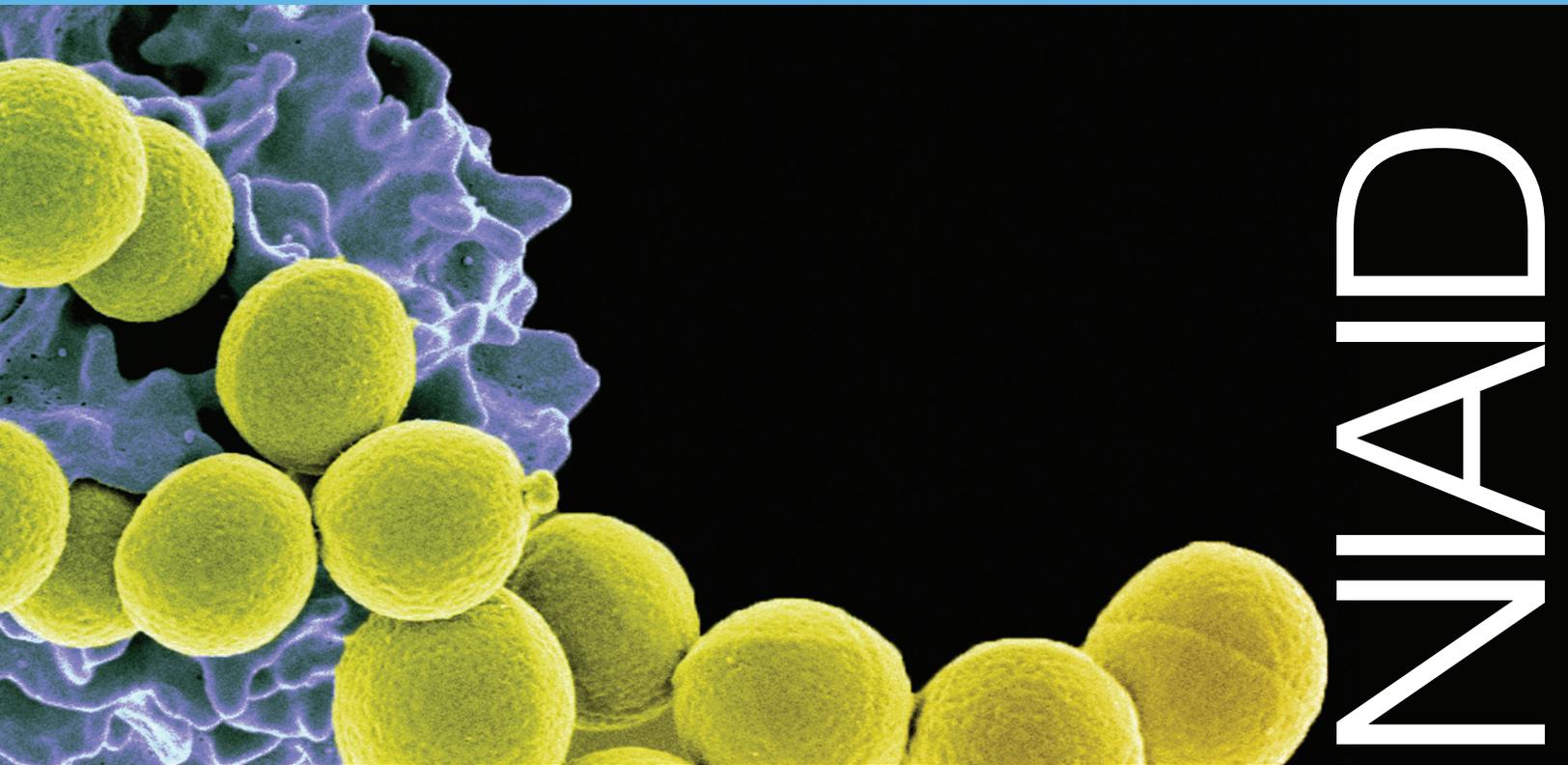


NIAID Strategic Plan 2013



NIAID

National Institute of Allergy and Infectious Diseases



National Institute of
Allergy and
Infectious Diseases

A Letter from the Director

Dear Colleagues:

For more than six decades, scientists supported by the National Institute of Allergy and Infectious Diseases (NIAID) have been at the forefront of important research in infectious and immune-mediated diseases, microbiology, immunology, and related disciplines. Their work has contributed to the development of new and improved medical tools to detect, treat, and protect against illness, alleviate suffering and prevent death in the United States and around the world.

The purpose of this document is to articulate the current strategic priorities of the Institute according to our four main scientific areas of emphasis: HIV/AIDS; Infectious Diseases (Non-AIDS), Including Emerging and Re-emerging Diseases and Biodefense; Allergy, Immunology, and Immune-Mediated Diseases; and Global Health Research. NIAID has built up a robust portfolio of basic, translational, and clinical research to sustain and advance these core areas. The Institute also has carried out its mandate to respond rapidly to emerging and re-emerging infectious diseases that occur periodically but unexpectedly. Since the publication of the last NIAID Strategic Plan in 2008, we have witnessed dozens of such threats to public health. The most prominent was the global 2009 H1N1 influenza pandemic, during which NIAID coordinated a series of clinical trials that led to the licensure of an effective vaccine against this new virus in just a few months. Other examples include the emergence of a novel pathogenic coronavirus, the increasing spread of dengue fever, and the development of multidrug-resistant gonorrhea and extensively drug-resistant tuberculosis.

Since 2008, however, we also have seen the rapid evolution of technological capabilities and research tools that offer an unprecedented range of new scientific opportunities. These tools include high-throughput genomic sequencing and bioinformatics, as well as the multidisciplinary approach to research known as systems biology. As always, although the fundamental mission of the Institute has not changed, we continually re-examine and update both our research approaches and our research priorities.

The 2013 NIAID Strategic Plan outlines our current research priorities that will help guide our future decision making. Strategic planning is especially important in our present environment of constrained research resources. In this regard, the 2013 Plan reflects increased opportunities for collaboration across our four major scientific areas of emphasis. With a strong research base, talented investigators in the United States and abroad, and the availability of powerful new research tools, we are confident that this Plan will help guide our research programs toward our ultimate goal of improving global health.

Sincerely,

Anthony S. Fauci, M.D.
Director, NIAID

The NIAID Mission

The mission of the National Institute of Allergy and Infectious Diseases (NIAID) is to conduct and support basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. Infectious diseases include global killers such as human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB), and malaria; emerging or re-emerging threats such as influenza, multiple drug-resistant tuberculosis (MDR TB), and methicillin-resistant *Staphylococcus aureus* (MRSA); and “deliberately emerging” threats from potential agents of bioterrorism. Immune-mediated disorders include autoimmune diseases, such as lupus and type 1 diabetes; asthma; allergies; and graft rejection and other problems associated with tissue and organ transplantation.

The strategic management of such a complex research mission has two core components: 1) maintaining a breadth and depth of knowledge in all areas of infectious and immune-related diseases, and 2) developing flexible domestic and international capacity to efficiently undertake research required in response to newly emerging threats wherever they occur.

To accomplish its mission, NIAID conducts and supports a comprehensive portfolio of research on the biology of pathogenic organisms, the host response to microbes, the mechanisms of normal immune function, and immune dysfunction that results in autoimmunity, immunodeficiency, allergy, and transplant rejection. This basic research provides the scientific understanding and research platform for translational and clinical research to develop and test vaccines, therapeutics, and diagnostics to prevent and treat the many infectious, immune-mediated, and allergic diseases that afflict people throughout the world.

After the events of September 11, 2001, and the subsequent release of anthrax spores, biodefense became an important element of the NIAID mission. In 2003, NIAID was assigned lead responsibility within the U.S. Department of Health and Human Services (HHS) and the National Institutes of Health (NIH) for civilian biodefense research. Since then, NIAID has supported research and early development of medical countermeasures against terrorist threats from infectious diseases and radiation exposure. NIAID later assumed responsibility for coordinating the NIH-wide effort to develop medical countermeasures against chemical threats to the civilian population. Because new potentially deadly pathogens, such as avian influenza, may be naturally occurring as well as deliberately introduced by terrorists, NIAID’s biodefense research is integrated into its larger emerging and re-emerging infectious diseases portfolio. While NIAID continues to focus on developing drugs, vaccines, and diagnostics for these disease agents, the research focus has evolved from the traditional “one bug–one drug” approach to a more flexible strategy using sophisticated genomic and proteomic platforms focused on developing broad-spectrum therapies effective against entire classes of pathogens.

NIAID is dedicated to building and sustaining a comprehensive research infrastructure to support its mission. Such infrastructure includes adequate, well-placed facilities for conducting research on highly infectious pathogens, and expertise to facilitate product development leading to approval by the U.S. Food and Drug Administration (FDA) of vaccines, therapeutics, and diagnostics. NIAID also supports an extensive clinical trials infrastructure. Recently, NIAID expanded the long-standing HIV/AIDS clinical trials networks to support critical research efforts on tuberculosis and hepatitis C, common co-infections in HIV-infected people. In addition, the Institute has established a new clinical trial network to address antibacterial resistance research, a growing public health concern. NIAID also fosters the organization of consortia, repositories, and databases, thus providing critical resources to support its scientific research. Finally, NIAID supports the training and professional development of scientists in the fields of infectious diseases and immunology.

Given the global impact of infectious diseases, a key aspect of the Institute's mission is to foster and maintain a strong program of international research and research capacity building. Clinical research on HIV/AIDS, TB, malaria, neglected tropical diseases, and other leading infectious causes of global mortality is best pursued through mutually beneficial partnerships that engage researchers and institutions in countries where these diseases are endemic. Thus, NIAID supports networks of U.S. and international scientists, trains American and foreign investigators to work internationally, and enhances research facilities around the world. NIAID recognizes that international research must involve shared leadership, a commitment to long-term sustainability, and the engagement of local communities if it is to contribute substantially to improvements in global public health.

An overarching priority in all NIAID research programs is to reduce health disparities and improve health for all people as research advances are translated into clinical practice. Many NIAID advances have helped to address health disparities. Examples include the development of effective therapies for hepatitis B and C virus infection and interventions to reduce the burden of asthma on children residing in inner cities. In addition, NIAID actively seeks the participation of diverse populations in clinical studies to ensure the scientific validity and broad applicability of research findings.

For nearly 60 years, NIAID research has led to new vaccines, therapeutics, diagnostics, and other technologies that have improved health and saved millions of lives in the United States and around the world. NIAID will continue to play a leading role in advancing knowledge of infectious and immune-mediated diseases and in accelerating the development of treatments and prevention strategies to respond to emerging public health threats.

Infectious Diseases (non-AIDS) Including Emerging and Re-emerging Diseases and Biodefense

Throughout history, infectious diseases have posed a major threat to human health. Their impact continues to be an important human health concern, in the United States and around the world. Although advances in medicine and public health—such as antibiotics, vaccines, and improved sanitation—have helped control many endemic diseases, infectious diseases remain the second leading cause of death throughout the world. In 2002, infectious diseases were the cause for more than one-quarter of approximately 57 million deaths worldwide.¹ Approximately two-thirds of all deaths in developing countries among children younger than 5 years of age² are due to infectious diseases.

New challenges arise continually, including the emergence of new infectious diseases, the re-emergence of drug-resistant bacterial strains, such as *Neisseria gonorrhoeae* and multi- and extensively drug-resistant TB, which are no longer responsive to traditional treatments; and the global persistence of respiratory, sexually transmitted, and enteric pathogens that can become epidemics.

Natural genetic variations also allow novel strains of known pathogens to appear, such as the 2009 outbreak of a new strain of H1N1 influenza A. NIAID support for influenza research over the past several years has greatly improved our preparedness for and ability to respond to a pandemic, and reaffirms that continued vigilance, planning, and strong biomedical research capability and public health response are essential defenses against emerging health threats.

Despite advances, many infectious diseases are not adequately controlled. Some that pose ongoing health problems in developing countries emerged recently in the United States, including food- and waterborne (e.g., *Shigella*) and vector-borne (e.g., West Nile virus) infections. Some diseases, such as Lyme disease, continue to be a problem in the United States. In addition, the resurgence of some diseases, such as TB, resulted from evolution of pathogen strains that are highly resistant to available treatments. Neglected tropical diseases (NTDs), such as dengue, lymphatic filariasis, trachoma, and leishmaniasis, are of particular concern. These infectious diseases take a tremendous toll on global health and can cause significant, lifelong disability.

Since the terrorist attacks of Sept. 11, 2001, and the subsequent anthrax mailings of that fall, NIAID has played a role in the national strategy to develop medical products and approaches to counter bioterrorism and emerging and re-emerging infectious diseases. NIAID supports basic research to better understand infectious agents and host-pathogen interactions. As described in NIAID's *Strategic Plan for*

¹ World Health Organization (WHO). *The world health report: 2004—Changing history*; <http://www.who.int/whr/2004/en/>.

² WHO. *The world health report: 2005—Make every mother and child count*; <http://www.who.int/whr/2005/en/index.html>.

Biodefense Research,³ NIAID's research has evolved from a focus on individual pathogens to a broad-spectrum approach to vaccines, diagnostics, and therapeutics that address multiple pathogens. This move from the "one bug–one drug" approach toward a more flexible, comprehensive strategy using sophisticated genomic and bioinformatics technologies is yielding numerous scientific advances and equips the nation with an integrated, coordinated approach to addressing public health crises.

NIAID's work is part of a national and international effort to reduce morbidity and mortality from infectious diseases, develop defenses against emerging or deliberately introduced infectious diseases, and improve public health around the world. NIAID partners with many organizations, including other government agencies, foundations, nonprofit organizations, foreign governments, and pharmaceutical and biotechnology companies.

Area of Emphasis: Biology of pathogens and host-pathogen interactions

NIAID supports basic research to elucidate pathogen biology; interactions among pathogens, hosts, and the environment; and the varied and ingenious ways that microbes survive and multiply. Discoveries made through basic research expand the biomedical knowledge base, lay the foundation for applied research, and pave the way for new treatment and prevention strategies. For example, NIAID's longstanding support of basic research studies of the hepatitis C virus (HCV) enhanced understanding of how HCV replicates, enabling the development of two new anti-HCV drugs and several promising drugs now being evaluated in clinical trials.

Several key NIAID efforts may lead scientists to identify potential new targets for therapeutics and vaccines. Scientists increasingly pursue systems biology approaches to identify host-pathogen interactions that help explain and predict clinical manifestations of infectious diseases, including disease progression and outcomes. Experimental technologies used include high-throughput genomics, transcriptomics, proteomics, metabolomics, and lipidomics, all of which enable scientists to examine biological processes of infectious diseases at the molecular level. Bioinformatics approaches are key to analyzing and understanding large data sets generated by these high-throughput technologies. NIAID-supported Bioinformatics Research Centers collect, integrate, and provide easy access to research data on microbial organisms and vectors of infectious diseases as well as novel analytical tools to facilitate data interpretation by the broader scientific community. NIAID also partners with other NIH Institutes and Centers to support the NIH Human Microbiome Project. The goal of this project is to enable comprehensive characterization of human microbiota and analyze their role in health and disease.

³ NIAID Strategic Plan for Biodefense Research (2007 update); <http://www.niaid.nih.gov/topics/BiodefenseRelated/Biodefense/Documents/biosp2007.pdf>

These enterprising research efforts continue to uncover the mysteries of infectious pathogens, and provide an important knowledge base that enhances our ability to identify and characterize newly emerging or re-emerging threats.

PRIORITY 1: Through basic research, increase understanding of the molecular structure and function of known viral, bacterial, fungal, prion, and parasitic pathogens and identify new pathogens.

PRIORITY 2: Use advanced technologies, including next-generation genomic technologies, to extend insights into mechanisms of infection, pathogenicity, virulence, host-pathogen interactions, and development of drug resistance for diseases such as TB.

PRIORITY 3: Characterize microbial communities throughout the human body in an effort to understand the role of the innate immune system in protecting the host from infectious pathogens.

PRIORITY 4: Determine the influence of co-infecting microbes on the pathogenesis of infectious diseases in order to better understand the impact of eliminating secondary infections on disease outcomes.

Area of Emphasis: Medical interventions

Insights from basic research often yield concepts for new vaccines, therapeutics, and diagnostics that are validated in model systems and then further developed and tested in applied research settings. Promising candidates advance through the research and development pipeline to human testing in clinical trials. NIAID supports studies throughout the development pipeline, from early discovery to clinical evaluations of candidate diagnostics, vaccines, and therapeutics.

Diagnostics

As infectious diseases continue to take their toll around the world, there is an urgent need for rapid, highly sensitive, and specific clinical diagnostics that are easy to use, cost-effective, suitable for use in point-of-care settings, and able to determine a pathogen's drug sensitivities. Many of the initial symptoms caused by bacterial, viral, or parasitic infections, or by exposure to toxins, may be nonspecific, making it difficult for clinicians to identify appropriate treatment options. The introduction of the Xpert MTB/RIF test for diagnosing TB, developed in part through NIAID support, addresses the urgent need for new tools to rapidly diagnose TB and its drug-resistant forms. This new test is expected to help stem the tide of new TB infections.

Researchers are using advanced technologies to identify diagnostic targets and develop new diagnostic methods. For example, NIAID-supported scientists are developing simple tests that can quickly and accurately determine whether a person is infected with *Borrelia burgdorferi*, the bacterium that causes Lyme disease. NIAID also supports research to develop multiplex platforms capable of detecting multiple pathogens and/or toxins in a single test. The multiplex diagnostic platform FilmArray®, developed with NIAID support and approved by the FDA, can detect 21 respiratory pathogens from patient samples and differentiate among particular influenza strains.

NIAID continues to support clinical validation of new infectious disease diagnostics. The Institute also supports studies to improve sample processing and preparation, decrease time to diagnosis, and develop instrumentation and platforms for primary healthcare settings.

PRIORITY 1: Conduct basic research, including using advanced genomics technologies, to develop a clearer understanding of pathogens, disease, and host immunity and to discover unique characteristics that could be used as specific and sensitive targets for preventing, diagnosing, monitoring, and treating infectious diseases.

PRIORITY 2: Develop and expand diagnostic platforms and technologies that can identify multiple pathogens, distinguish pathogen strains, recognize early infection or exposure, and detect drug sensitivity and resistance. These platforms and technologies must be reliable, rapid, sensitive, specific, cost-effective, and easy to use in a variety of settings.

Vaccines

Vaccines have led to many of the greatest improvements in public health. Exciting developments in vaccine research methodology are emerging as scientists improve their understanding of the immune system and how it fights harmful microbes. These advances lead to clinical trials to evaluate candidate vaccines developed to protect against diseases such as malaria and influenza. Many of these trials are conducted through NIAID's longstanding Vaccine and Treatment Evaluation Units (VTEUs). NIAID is expanding the VTEUs to enable the conduct of studies in disease-endemic areas. Technological advances continue to improve existing vaccines and allow identification of vaccine candidates to prevent diseases for which no vaccines are currently available. For example, NIAID is conducting a trial to evaluate the safety, immune response, and initial efficacy of a vaccine to prevent acute and chronic hepatitis C infection.

As new pathogens and novel strains of existing pathogens emerge, new vaccines are needed, and NIAID will continue responding to this challenge through vaccine research. An integral part of this challenge is the quest to better understand innate and adaptive immune responses and advance the development of cross-protective vaccine strategies. NIAID's funding for projects focused on the development of a universal influenza vaccine illustrates the commitment to cutting-edge vaccine research.

PRIORITY 1: Conduct basic research to elucidate mechanisms of host-pathogen interactions, to better understand and enhance immune responses, and to identify promising new vaccine targets for diseases of global health importance.

PRIORITY 2: Design new or improved vaccines that are safe and effective, with particular emphasis on multivalent and cross-protective vaccine strategies such as a universal influenza vaccine.

PRIORITY 3: Use advanced technologies to rapidly determine safety and immunogenicity of candidate vaccine products and to streamline manufacturing.

PRIORITY 4: Support the advanced development of candidate vaccines that are easy to deliver, produce protective immunity with fewer doses of vaccine, and are readily stored and easily distributed.

Therapeutics

NIAID supports a variety of approaches to identify potential targets for intervention and to engineer new therapeutics. The ability of pathogens to develop drug resistance makes establishing an arsenal of safe and effective antimicrobials especially challenging, particularly for many of the NTDs for which only limited drug regimens are available. Exciting progress is being made by screening existing products for activity against different pathogens, or, in the case of malaria, by combining new or existing compounds into better multidrug regimens. In the area of biodefense, NIAID-supported animal model studies played a major role in the FDA decision to approve levofloxacin to treat and prevent pneumonic plague. Rising rates of antimicrobial resistance are another area of concern. NIAID supports multiple clinical trials designed to provide vital information on the optimal use of currently available antibacterial drugs. The goal is to find treatment regimens that limit the emergence of drug resistance. Identifying and approving new uses for existing antimicrobials will facilitate an effective response in the event of a public health emergency. For example, such medications can be stored in the Strategic National Stockpile, a national repository of life-saving pharmaceuticals and medical supplies that may be dispensed to meet urgent public health needs.

While repurposing existing drugs holds promise, new treatments that are effective against a range of pathogens are also needed. This broad-spectrum approach would allow a small number of drugs to replace dozens of pathogen-specific drugs, thereby improving preparedness for all infectious threats, whether naturally occurring or deliberately introduced (i.e., bioterror threats).

PRIORITY 1: Conduct basic research to understand how pathogens develop drug resistance.

PRIORITY 2: Identify potential targets for developing novel approaches to broad-spectrum interventions.

PRIORITY 3: Identify new strategies for developing immunotherapies, including those based on host responses.

PRIORITY 4: Use advanced technologies to screen, test, and develop novel and improved chemotherapies, biopharmaceuticals, and immunotherapies that offer broad-spectrum coverage.

PRIORITY 5: Conduct clinical research to investigate new strategies for using existing drugs to limit antimicrobial resistance.

Global Health Research

For nearly 60 years, NIAID research has led to new vaccines, diagnostics, and therapeutics that improved the health of millions of people in the United States and around the world. International research at NIAID addresses a multitude of infectious diseases that cause millions of death worldwide each year, such as TB and malaria. These research activities span the spectrum from basic through applied research. Research conducted in international settings can enable scientists to conduct studies in disease-endemic areas and benefit populations most affected by particular diseases. NIAID does not

target specific countries or geographical regions for funding. The Institute recognizes, however, that this solid foundation of global health research and collaboration enhances capacity for infectious disease surveillance and the ability to respond to newly emerging threats, including diseases with potential to cause global pandemics, such as influenza. Moreover, NIAID has employed creative solutions to address global health priorities, such as supporting the discovery and development of drugs for NTDs through public-private partnerships in collaboration with non-federal entities.

PRIORITY 1: Continue to build a solid base of diverse research expertise to quickly address the emergence and re-emergence of new and existing infectious diseases around the globe.

PRIORITY 2: Support the participation of international investigators in the conduct of infectious diseases research in order to enhance our understanding of these diseases in their natural environments.

PRIORITY 3: Continue to support existing partnerships and develop new collaborations with institutions and organizations involved in global research. Partnerships and collaborations enable NIAID to leverage its resources for international research.

For more information, please see the section on Global Health Research.

Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome

Extraordinary progress has been made in HIV/AIDS research since the disease was first noted in published case reports more than 30 years ago. Researchers now understand HIV and its pathogenesis, can rapidly and specifically diagnose HIV infection, and can profoundly suppress HIV replication with highly active antiretroviral therapy (HAART). These potent antiretroviral drugs have saved an estimated 3 million years of life in the United States alone⁴, nearly eliminated mother-to-child transmission (MTCT) of HIV infection in many parts of the developed world, and reduced the incidence of HIV infection in some developing-world settings.

HAART also effectively prevents sexual transmission of HIV in adults, as demonstrated by results from the HIV Prevention Trials Network Study 052 (HPTN 052).⁵ This NIAID-supported study evaluated whether antiretroviral drugs can prevent the sexual transmission of HIV among couples in which one partner is HIV-infected and the other is not (sero-discordant couples). The study found that if HIV-infected heterosexual individuals begin taking antiretroviral medicines when their immune systems are relatively healthy—rather than delaying therapy until the disease has advanced—they are as much as 96 percent less likely to transmit the virus to their uninfected partners. *Science* selected this landmark study as the 2011 Breakthrough of the Year.

Recognizing the considerable advances made in HIV/AIDS research and the opportunity to build on these advances, Secretary of State Hillary Clinton unveiled a blueprint for an “AIDS-free generation” in November 2012. The blueprint focuses on preventing new HIV infections and stemming the progression of HIV infection to AIDS in infected persons. In addition to this goal, scientists are working to truly control and ultimately end the HIV and AIDS pandemic by curing HIV infection.

Transformative successes in HIV prevention will require multiple versions of combination prevention strategies that are well-suited to specific target populations. A safe and effective HIV vaccine has long been, and continues to be, a major goal of HIV-prevention research domestically and internationally. Researchers now see the vaccine as an essential complement to combinations of existing prevention strategies that will curtail the HIV/AIDS pandemic. Developing an effective HIV vaccine has been particularly challenging; an HIV vaccine must show significant and durable protection against all methods of transmission and all clades and strains of HIV. New biomedical prevention tools that can be

⁴ Vermund SH. *J Infect Dis.* 2006 Jul 1; 194(1):1-5.

⁵ M.S. Cohen *et al.* Prevention of HIV-1 Infection with Early Antiretroviral Therapy. *New England Journal of Medicine* DOI: 10.1056/NEJMoa1105243 (2011).

integrated with or enhance currently available prevention strategies are also needed. All of these prevention tools must be linked with social and behavioral interventions.

As NIAID joins international partners in aggressively pursuing research to control and ultimately end the HIV/AIDS pandemic, the Institute's HIV/AIDS research agenda increasingly addresses common co-infections, such as TB in global populations and hepatitis globally and domestically.

Area of Emphasis: Halt the spread of HIV infection by defining highly effective prevention strategies, including a preventive HIV vaccine

The most compelling goal in HIV research is prevention of HIV infection, which is critical to the long-term goal of controlling and ultimately ending the HIV pandemic. While scientists are making progress, an HIV vaccine is likely still years away. Importantly, a number of prevention methods with a strong evidence base already exist, including proper use of condoms, needle exchange, adult male circumcision, pre-exposure prophylaxis (PrEP), and treatment as prevention (TaP). Lack of HIV testing and linkage to care must be addressed in order to advance TaP from a proof of principle in a clinical trial to a viable public health intervention. Identifying HIV-infected people through HIV testing is the single most important step toward improving the impact of treatment, care, and prevention services. For testing to be maximally effective it must be provided routinely, and, when an HIV-positive person is identified, linkage and retention in care must occur quickly and seamlessly. This “test and treat” concept is currently under investigation through the HPTN 065 study, TLC-Plus: A Study to Evaluate the Feasibility of an Enhanced Test, Link to Care, Plus Treat Approach for HIV Prevention in the United States.

On a global scale, these proven prevention approaches, alone or in combination, are accessible to only a fraction of those who would benefit from their implementation. Devising ways to scale up proven, integrated prevention methods would have an important impact on the HIV epidemic. Implementing these prevention methods, along with effective social mobilization and behavioral interventions, must be bolstered by developing and validating additional, potent prevention tools, such as antiretroviral therapy (ART)-based prevention strategies and a safe and effective HIV vaccine. All future prevention research must integrate an understanding of behavioral factors, adherence, and acceptability at the earliest stages of product discovery.

PRIORITY 1: Devise strategies to block HIV infection at mucosal surfaces and other tissues by defining the early steps in HIV acquisition that lead to the establishment and systemic spread of HIV.

PRIORITY 2: Study the interaction of HIV with the human immune system at the organism level through the integrated use of bioinformatics, computational approaches, and systems biology to better understand how the virus causes disease and what aspects of the host influence vulnerability to infection.

PRIORITY 3: Establish pathways for rational development of effective HIV vaccines by building a better foundation of basic knowledge about innate and adaptive immune responses to HIV infection and to experimental vaccines.

PRIORITY 4: Drive research to discover safe and effective vaccine candidates, including:

- Following up on the results of the Thai Phase III HIV vaccine trial, also known as RV144, to capitalize on the only demonstration of vaccine efficacy to date and attempt to expand potency and durability
- Facilitating rational, structure-driven vaccine design
- Developing strategies to optimize the evaluation of B-cell responses
- Identifying vaccine adjuvants and immune modulators that enhance vaccine activity and extend the breadth and/or duration of the protective immune response

PRIORITY 5: Design and conduct clinical trials that demonstrate the safety and efficacy of HIV vaccine candidates by:

- Building on the success of existing vaccines to create more effective vaccines
- Expediting the identification and evaluation of immunogens
- Efficiently assessing vaccine effect
- Rapidly assessing potential correlates of immunogenicity and of protection elicited by experimental vaccines
- Producing a vaccine that is effective for various risk groups and demographics and protects against different modes of transmission

PRIORITY 6: Advance a comprehensive research program aimed at developing and evaluating safe, effective, and acceptable non-vaccine prevention methods and optimal formulations, dosage, and product delivery methods, including but not limited to topical microbicides and pre- and post-exposure prophylaxis.

PRIORITY 7: Establish partnerships to better understand biologic-behavioral interactions and devise and test optimal combination HIV prevention packages (combination interventions) for specific settings and populations.

PRIORITY 8: Collaborate with other institutes and organizations, both domestic and international, to characterize acceptability, adherence, durability, and optimal delivery modes of prevention interventions.

Area of Emphasis: Cure HIV Infection

ART can be extremely effective in suppressing detectable viral replication for extended periods, but no documented cases of a true cure have occurred in the 30-year duration of the HIV epidemic. It is claimed that one HIV-infected individual was “cured” after receiving stem-cell transplants for a complicating leukemia. The transplanted cells expressed a genetic defect that does not allow the replication of R5 HIV viruses. This case, while not a practical approach for treating the millions of HIV-infected people, provides proof of concept that under certain circumstances HIV can be controlled in the absence of ART.

When considering a cure for HIV infection at least two related lines of research should be considered: 1) developing a true sterilizing cure, with complete eradication of the virus; and 2) permanently suppressing the virus such that there is no significant replication even in the absence of ART, i.e., a functional cure. A cure for HIV infection must be safe, scalable, and less traumatic to patients than current treatment regimens.

PRIORITY 1: Broaden understanding of the basic biology of both latent and persistently replicating HIV reservoirs by:

- Determining if additional reservoirs of HIV infection exist
- Defining the processes that govern reservoir establishment and maintenance
- Understanding the mechanisms of persistence in persons receiving effective ART

PRIORITY 2: Develop methods to accurately measure the reservoir in patients.

PRIORITY 3: Identify and test concepts or strategies for eradication of HIV reservoirs.

PRIORITY 4: Explore methods of establishing a functional cure that would allow subjects to discontinue antiretroviral treatment for extended periods without viral rebound.

PRIORITY 5: Clinically test novel strategies that target and eliminate viral reservoirs or bring about a functional cure.

Area of Emphasis: Establish treatment and prevention strategies for HIV-associated infections of highest morbidity and mortality, especially TB and hepatitis

AIDS-associated co-infections are potentially life-threatening conditions caused by a wide range of microorganisms, including protozoa, viruses, fungi, and bacteria. HIV-associated co-infections such as TB and hepatitis C complicate the medical management of HIV-infected people and result in significant morbidity and mortality, especially in resource-limited settings. HIV infection is a risk factor for conversion of latent TB infection to active TB, and TB accelerates the progression of HIV to AIDS. Furthermore, TB is harder to diagnose and progresses faster in HIV-infected people. TB is the cause of death for as many as half of all people who are co-infected with HIV. Similarly, co-infection with HCV has been associated with decreased effectiveness of ART and higher rates of morbidity and mortality. Current treatment of HCV is not well tolerated in HIV-infected patients on ART and not very effective. Newer agents to treat hepatitis C are being developed and will need to be investigated in the co-infected population. Researchers are working to determine when best to initiate ART in persons with active co-infections in order to maximize the effects of treatment and minimize the risks of immune reconstitution inflammatory syndrome.

PRIORITY 1: Elucidate the pathogenic mechanisms and consequences of high-priority co-infections in the context of HIV infection through epidemiological and clinical research.

PRIORITY 2: Expand understanding of TB as an HIV-associated infection by:

- Developing improved diagnostics and prognostic biomarkers for TB (in all age groups)
- Advancing improved and/or shorter-course combination drug therapy for both active and latent TB (including drug-sensitive and drug-resistant TB)

PRIORITY 3: Facilitate large-scale efficacy testing of promising TB treatments and vaccines through coordination with HIV clinical trials capability.

PRIORITY 4: Expand research for infectious hepatitis as an HIV-associated infection by:

- Developing all-oral treatment regimens that cure HCV and are safe and well tolerated
- Developing improved diagnostics, noninvasive indicators of liver injury, and prognostic biomarkers for treatment outcomes
- Identifying pathways and mechanisms that accelerate the course of HCV disease in HIV co-infected individuals

PRIORITY 5: Support clinical studies of other high-priority co-infections to improve diagnostic, treatment, and prevention strategies.

Area of Emphasis: Improve outcomes of treated HIV disease

The greatest achievement in HIV research has been the discovery, development, and delivery of ART to millions of HIV-infected people. Treatment blocks further disease progression, preserves remaining immune function, and can also prevent HIV transmission. This advance creates areas of research synergy where improvements in the delivery of HIV testing and care can have a profound benefit for HIV-negative and positive people alike. Continuing to improve the safety and durability of therapeutic regimens will also enhance the treatment and prevention effects of ART. Through focused research to define how best to use these tools, we can begin to control the global HIV epidemic.

PRIORITY 1: Define long-term consequences of treated HIV infection and the mechanisms of morbidity associated with treated HIV disease.

PRIORITY 2: Develop understanding of chronic immune activation and associated co-morbidities in HIV-infected individuals who are on suppressive ART through:

- Research of basic pathways and mechanisms
- Use of animal models of chronic inflammation as models for pathogenesis due to chronic immune activation and for preclinical studies of possible interventions

PRIORITY 3: Develop and evaluate potential therapies to eliminate or suppress immune activation and associated clinical consequences.

PRIORITY 4: Explore the role of HIV in the development of premature aging of the immune system in HIV-infected individuals on suppressive ART.

PRIORITY 5: Discover and evaluate novel interventions, long-acting formulations, and drug delivery technologies to diagnose and treat HIV, leading to significant, durable improvements in therapy.

Global Health Research on HIV/AIDS

NIAID supports a broad portfolio of international research on HIV/AIDS that reflects the global impact of the disease. This research addresses the critical need for cost-effective prevention and treatment strategies, particularly in areas of the world with limited resources and where more than 95 percent of HIV infections occur.

Examples of major ongoing international clinical studies include:

- The Promoting Maternal and Infant Survival Everywhere (PROMISE) study, which is designed to determine the best treatment regimen for: 1) preventing antenatal mother-to-child transmission (MTCT), 2) preventing MTCT during breastfeeding, 3) maintaining the health of the mother, and 4) protecting the infant during weaning in high-, middle-, and low-resource settings. The study will enroll approximately 8,000 HIV-infected women who are pregnant or have recently given birth and approximately 6,000 HIV-exposed infants from as many as 18 countries.
- A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), which is a Phase III microbicide study to determine whether a woman's use of a vaginal ring containing the antiretroviral drug dapivirine is safe and effective for protecting against HIV infection. The study will enroll approximately 3,500 women at several sites in Africa and is expected to be completed in 2014.
- The Strategic Timing of Antiretroviral Treatment (START) trial, which is a randomized clinical trial designed to provide definitive evidence of the risks and benefits of early antiretroviral treatment and to more clearly define the optimal time to begin treatment. The study is being conducted in 30 countries and will enroll approximately 4,000 HIV-infected men and women who are 18 years of age and older, have CD4 counts above 500 cells/mm³, and have never taken antiretroviral drugs.

NIAID also funds the International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium, which is composed of seven regional databases in the Caribbean, Central and South America region; North America; West Africa; East Africa; Central Africa; Southern Africa; and Asia/Australia/China. IeDEA collected and analyzed data from more than 1 million patients. This wealth of information enabled IeDEA to contribute substantially to the effort to evaluate and describe the roll-out of therapy around the world, define outcomes for adult and pediatric patients, evaluate the success of programs in care and treatment delivery, define new approaches to managing care in resource-limited settings, and describe the epidemiology of cancer in HIV-infected persons around the world.

The expansion of HIV care and treatment to the developing world is a major success in ongoing efforts to address the HIV/AIDS epidemic. The President's Emergency Plan for AIDS Relief (PEPFAR), initiated in 2003 by President George W. Bush, together with the multilateral Global Fund to Fight AIDS, Tuberculosis and Malaria and non-government organizations such as the Bill & Melinda Gates Foundation, the Clinton Foundation, and Médecins Sans Frontières (Doctors Without Borders), have transformed the fate of countless HIV-infected people in the developing world, particularly southern Africa, by providing treatment and care for those who are infected as well as prevention methods for those at risk of infection. As of September 2012, PEPFAR alone had provided ART for more than 5 million infected individuals; provided antiretroviral mother-to-child transmission prevention for more than 750,000 HIV-infected pregnant women; and provided care for approximately 15 million people, including AIDS orphans.⁶ Yet even with current efforts, approximately 2.5 million people become infected with HIV each year, and for every two people that begin treatment with ART, five become newly infected. NIAID helps support PEPFAR by providing staff management and oversight support for

⁶ U.S. Department of State. PEPFAR Blueprint: Creating an AIDS-free Generation, Nov 2012; <http://www.pepfar.gov/documents/organization/201386.pdf>

supplements to existing NIAID grantees and other NIH Institutes and Centers (ICs). Most recently, in collaboration with the Office of the Global AIDS Coordinator and other ICs, NIAID established the NIH/PEPFAR Collaboration for Implementation Science and Impact Evaluation program to support research studies to help inform PEPFAR on more efficient and cost-effective methods to deliver HIV prevention, treatment, and care on a large scale in resource-limited countries.

PRIORITY 1: Establish, enhance, and build on the in-country research capacity of low- and middle-income countries. The aim is for these nations to develop sustainable research programs focused on developing biomedical strategies to prevent transmission of HIV and to treat HIV disease and its associated co-infections and co-morbidities.

PRIORITY 2: Assist in developing vaccines, other prevention strategies, and therapeutic interventions that reflect local population/regional determinants, processes, and cultural and contextual issues and that will be widely affordable, accessible, and practical in those settings.

For more information on NIAID's global health research, please see the section on Global Health Research.

Partnerships

The development and testing of successful therapies, diagnostics, and prevention technologies relies on partnerships between the Institute and the private sector. NIAID invests in the development of biomedical research capacity around the world by fostering research collaborations between U.S. and international scientists, many of whom are based in developing countries. For example, through an Interagency Agreement, NIAID collaborates with the Department of Defense's U.S. Military HIV Research Program (MHRP) to support and conduct relevant clinical research and evaluation of candidate HIV vaccines worldwide. This partnership led to the first HIV vaccine trial (RV144) to demonstrate modest efficacy, which in turn led to the creation of the Pox-Protein Public-Private Partnership (P5). The P5 is a collaboration of key funders and implementers of HIV vaccine research, which aims to conduct research critical to advancing and ultimately licensing HIV pox-protein vaccine candidates that have the potential to achieve broad public health impact. Partners of P5 include NIAID, MHRP, the Bill & Melinda Gates Foundation, the HIV Vaccine Trials Network, Sanofi Pasteur, Novartis, and Eurovacc. By partnering with academia, private industry, philanthropic foundations, and other research-supporting agencies, NIAID is able to guide, enhance, and support ongoing HIV/AIDS research activities around the world.

HIV infection is associated with significant end-organ morbidity, such as endothelial damage, neurocognitive defects, and renal failure. To understand the pathogenic mechanisms and to test interventions, NIAID partners with other ICs to fund research in these areas. Furthermore, strong psychological, sociological, and structural factors combine to create vulnerabilities that promote HIV transmission and worsen the AIDS epidemic. Interventions to address these vulnerabilities require integration of behavioral and biomedical expertise at all stages of research. The results of recent prevention trials highlight this need and underscore the importance of collaborating with other ICs that have a significant investment in behavioral research. Once effective interventions have been developed and licensed, other government agencies, such as the Centers for Disease Control and Prevention (CDC),

Health Resources and Services Administration, Office of the Global AIDS Coordinator, and U.S. Agency for International Development, are critical partners in designing research on the best approaches for implementing and scaling-up those interventions.

PRIORITY 1: Enable and encourage collaborations across public- and private-sector partners to optimize efficient use of resources including facilities, expertise, data and data analysis, specimens, reagents, and access to populations.

PRIORITY 2: Foster and support community involvement to ensure that communities heavily impacted by HIV/AIDS participate in all stages of planning and implementing HIV/AIDS research.

Allergy, Immunology, and Immune-Mediated Diseases

The human immune system has evolved to protect against harmful pathogens in the external environment. The ability to recognize pathogens and distinguish them from one's own cells and tissues is the first requirement of such a protective system. This task of distinguishing "self" from "non-self" initially falls to the innate immune system: the inborn capacity to constantly monitor the body's fluids, cells, and tissues for pathogens and provide a broad and immediate immune response. The innate immune system also activates the adaptive immune system, which, over time, generates unique T and B cells that specifically target a pathogen invading the body. Once the pathogen is cleared from the body, the immune system returns to its resting state, leaving behind long-lasting antibodies and a small number of memory T and B cells that can quickly reactivate if the pathogen reappears. Vaccines harness the innate and adaptive responses by partially mimicking a natural infection, but without causing disease. As with most naturally occurring infections, vaccines stimulate the formation of antibodies and memory cells that protect in the event of true infection.

Over the course of a lifetime, many immune responses arise that are potentially detrimental. These responses can lead to a wide range of immune-mediated diseases in susceptible individuals. For example, generally innocuous or harmless substances, including house dust mites, pollen, or foods such as peanut, activate the immune system, leading to asthma and allergic diseases. When the ability to distinguish self from non-self fails, autoimmune diseases occur. In organ transplantation, the recipient's immune system recognizes the donor organ as non-self, resulting in rejection of the transplant.

Asthma

A 2012 report⁷ from the CDC showed that the prevalence of asthma in the United States increased from 7.3 percent to 8.4 percent between 2001 and 2010, and an estimated 25.7 million people, including 7 million children, had asthma in 2010. African Americans had the highest prevalence rates and children and adolescents under 18 had higher rates than adults. Among individuals whose family income was below the federal poverty level, the prevalence of asthma was 53 percent higher than that for individuals whose family income was at least twice the poverty level. Overall, asthma is associated with an estimated \$56 billion in healthcare costs and lost productivity in the United States each year.⁸

Allergic Disease

Allergic diseases include a wide range of chronic illnesses, including food allergies. The prevalence of allergic rhinitis—more commonly known as hay fever—is 7.8 percent in adults aged 18 and older and 9.8

⁷ National Health Care Surveys Data Brief, Number 94. May 2012. Trends in Asthma Prevalence, Health Care Use, and Mortality in the United States, 2001-2010.

⁸ Centers for Disease Control. CDC VitalSigns: Asthma in the US, May 2011; <http://www.cdc.gov/vitalsigns/asthma/>

percent in children.^{9,10} According to the CDC,¹¹ 3.9 percent of children under age 18 (3 million people) reported having food allergy in the previous 12 months, and the prevalence of food allergy increased by 18 percent from 1997 to 2007, with peanut allergy increasing substantially. Children with food allergy are two- to four-fold more likely to have other allergic diseases, such as asthma, atopic dermatitis, and respiratory allergy, than children without food allergy.

Autoimmune Disease

More than 80 autoimmune diseases have been identified, and collectively they are estimated to affect five to seven percent of people in the United States (15 to 24 million people). Many of these diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), disproportionately affect women, especially during their childbearing years. These diseases are chronic and often debilitating, and associated medical and other social costs are high.¹² Examples of prevalence include:

- 15,600 youth under the age of 20 in the United States were newly diagnosed with type 1 diabetes each year for the years 2002 to 2005, and approximately 1 in every 400 to 500 children and adolescents had the disease.¹³
- An estimated 1.5 million Americans have RA.^{14,15}
- As many as 322,000 Americans have been diagnosed with, or are suspected of having, SLE,¹⁶ which disproportionately afflicts African American women.

Many other autoimmune diseases are rare and largely unknown, but, collectively, they affect a large number of people. In all cases, although treatments may alleviate symptoms, there are no cures, and the incidence of many autoimmune diseases appears to be increasing for reasons that are poorly understood.

Research on Immune-Mediated Diseases

The NIAID mission encompasses basic, preclinical, and clinical research on the causes, treatment, and prevention of a wide range of immune-mediated disorders. Across this spectrum, NIAID-sponsored research is contributing to fundamental discoveries that will lead to comprehensive understanding of the mechanisms involved in immune regulation and immune protection, with wide application in the development of vaccines and therapies for immune-mediated disorders.

⁹ [Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2009, tables 3 and 4.](#)

¹⁰ [Summary Health Statistics for U.S. Children: National Health Interview Survey, 2009, table 2.](#)

¹¹ [NCHS data brief no.10, NCHS, Sept 2008.](#)

¹² The Autoimmune Diseases Coordinating Committee, NIH: [Progress in Autoimmune Diseases Research 2005](#) (NIH Pub. No. 05-5140).

¹³ [National Diabetes Fact Sheet, 2011](#) (Source: CDC).

¹⁴ Myasoedova E et al., [Arthritis Rheum. 2010 Jun;62\(6\):1576-82.](#)

¹⁵ Helmick CG et al., [Arthritis Rheum 58\(1\):15-25, 2008.](#)

¹⁶ Laurence RC et al., [Arthritis Rheum 41: 778, 1998.](#)

Research on asthma and allergic diseases focuses on preventing detrimental immune responses to generally innocuous or harmless substances. Research on autoimmune disease aims to identify ways to “re-educate” the immune system so that it becomes tolerant to the “self” antigens and tissues that are the targets of attack. In organ transplantation, which prolongs survival and improves the quality of life for people suffering from a wide range of end-stage organ diseases, research aims to selectively block immune responses directed against the foreign antigens of the graft to allow long-term graft survival without the risks of broadly immunosuppressive therapies.

NIAID’s robust research portfolio in basic immunology provides fundamental insights into the principles of immunology and identifies the cells, molecules, and pathways of the immune system. For many years, scientists have relied heavily on inbred mouse models because of their ease of use and the wide availability of many mouse-specific laboratory reagents. These models are highly successful tools for the discovery of immunologic mechanisms that allow dissection of interconnected pathways with a high degree of resolution. In addition, genetic analysis has shown that there is considerable conservation of genes and gene regulation between mice and humans. Findings in mouse studies are not always reproducible in human studies, however, and it is clear that mice have considerable limitations as models of human disease and for drug discovery and development. Therefore, a major challenge in immunology is to characterize the human immune system in health and disease to provide a solid foundation for the translation of basic research into clinical research.

To meet this challenge, the NIAID research portfolio has evolved to include increased emphasis on human immunology. This is enabled by the emergence of new technologies, advances in systems biology approaches, expanding capabilities in bioinformatics, and the development of sophisticated data analysis tools. Together, these offer unprecedented opportunities to measure immune responses in individuals and large human cohorts. Recognizing the opportunities, NIAID has initiated new programs in human immunology that will increase our understanding of the causes of immune-mediated diseases and lead to the development of strategies for their prevention, diagnosis, and treatment. In addition, these studies will lead to more effective vaccination and other prevention strategies for infectious diseases.

NIAID’s clinical trial networks remain in the forefront of clinical immunology research, and strongly emphasize studies of asthma, allergy, autoimmune diseases, and the immune-mediated rejection of transplanted organs. The networks evaluate a variety of treatment and prevention strategies, including immune tolerance induction, withdrawal from immunosuppressive therapies, and immune modulation. All network studies include mechanistic studies to better understand the clinical outcomes. Notable science advances include the development of novel immunotherapeutic approaches that show promise in the treatment and prevention of food allergy; FDA approval of the first treatment for Wegener’s granulomatosis and microscopic polyangiitis, two rare forms of autoimmune disorders; and the demonstration that 60 percent of pediatric liver transplant recipients remain rejection free for 5 years after the withdrawal of immunosuppressive drugs.

In addition to the broadly stated priorities presented in this section and the published documents that were listed in [NIAID: Planning for the 21st Century 2008 Update](#), two published documents focus on specific goals. These documents include:

- [NIAID Strategic Plan for Research on Vaccine Adjuvants \(2011\)](#)
- [Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats Progress Report: 2005–2011 and Future Research Directions: 2012–2016](#)

Area of Emphasis: Apply knowledge of basic immunology to support preclinical research in infectious and immune-mediated diseases

Building on an increased understanding of the human immune system, NIAID supports a robust portfolio of applied immunology research that provides preclinical information critical for developing and evaluating novel strategies to diagnose, treat, and prevent infectious and immune-mediated diseases. A major scientific area with critical need is the development of new vaccines to protect against emerging or re-emerging infectious diseases, and the improvement of current vaccines, especially to protect populations such as the very young, the elderly, and those with compromised immune responses. Therefore, in recent years, NIAID launched, and is continuing to expand, programs to discover and develop adjuvants—components of vaccines that stimulate the immune response. NIAID also has increased its focus on the mucosal immune system, initiating programs to improve our understanding of its unique protective mechanisms and to develop targeted mucosal vaccines against infection. As part of its commitment to improving transplant outcomes, the Institute also supports programs to identify biomarkers of transplant rejection and characterize gene variants and expression patterns that predict transplantation outcome.

PRIORITY 1: Continue supporting research in basic immunology.

PRIORITY 2: Apply increasing knowledge of the complex interactions between microbes and the immune system to develop and test diagnostics, therapeutic strategies, and vaccine strategies for infectious diseases.

PRIORITY 3: Advance promising adjuvant candidates through optimization and preclinical testing.

PRIORITY 4: Apply knowledge of the processes and events that occur at mucosal surfaces to facilitate the design of vaccines and immunotherapies that protect mucosal surfaces from infection and disease.

PRIORITY 5: Evaluate reagents for the development of diagnostics, immunotherapeutics, and vaccines against infectious diseases and immune-mediated diseases.

PRIORITY 6: Develop novel strategies to prevent, treat, and detect immune-mediated diseases.

PRIORITY 7: Develop and enhance approaches through preclinical research to extend the survival of transplants.

Area of Emphasis: Determine the precise mechanisms of human immune regulation

Recognizing the recent advances in biotechnology and bioinformatics and the opportunities they offer, NIAID has increased its support of human immune studies within its basic immunology portfolio. In 2010, for example, NIAID established seven U.S. research centers comprising the Human Immunology Project Consortium (HIPC). HIPC investigators are using new research approaches to better understand the human immune system in health and in response to infection and vaccination. HIPC also has been supported to expand its focus internationally through research partnerships in India and elsewhere. In addition, NIAID supports and collaborates with the trans-NIH Center for Human Immunology, which uses novel technologies to translate our understanding of immune function and pathophysiology to clinical practice. These and other programs in basic human immunology are providing answers to fundamental questions about the components of our immune system and how they interact in health and disease.

PRIORITY 1: Further characterize the human innate and adaptive immune systems, both at rest and in response to infection and vaccination and as a consequence of immune-mediated disease.

PRIORITY 2: Identify the underlying genes and develop new approaches to analyze the cellular and molecular pathways involved in maintaining the human immune system at rest and after activation.

PRIORITY 3: Analyze the influence of the human microbiome on mucosal and systemic immune responses, and on the outcome of infectious diseases and immune-mediated diseases.

Area of Emphasis: Develop immune-based and tolerogenic approaches to treat and prevent allergic and autoimmune diseases and to prevent graft rejection

NIAID's clinical studies encompass a broad range of immune-mediated disorders, including asthma, allergic and autoimmune diseases, primary immunodeficiency disorders, and transplant rejection. All clinical trials include associated mechanistic studies to further our understanding of disease onset and progression and response to therapy. Various biological agents and novel approaches to induce and restore immune tolerance show promise in clinical trials and will continue to be pursued. These include cellular immunotherapeutics, which are potent immune cells that can be engineered to localize to specific organs and tissues and may eventually provide long-lasting efficacy and specificity unattainable with many drugs.

PRIORITY 1: Clinically evaluate anti-inflammatory, immunomodulatory, and immune tolerance approaches to prevent and treat immune-mediated diseases.

PRIORITY 2: Support integrated mechanistic studies with clinical trials to better understand the role of immune factors in immune-mediated disease susceptibility, disease progression, and treatment outcome.

PRIORITY 3: Support clinical evaluations of immune-based treatment, tolerance approaches, and other strategies to improve transplant survival and prevent graft rejection.

Essential Foundations for the Future

The biomedical advances made possible by NIAID-supported research increasingly depend on flexible and comprehensive infrastructure as products move from basic laboratory findings to preclinical models, product development, clinical trials, and, ultimately, licensure. Indeed, research resources and physical infrastructure underpin the full spectrum of NIAID-supported biomedical exploration and discovery. NIAID aggressively develops technologies needed to advance its mission, and makes these critical resources available to grantees in the United States and in international settings. Research infrastructure requires substantial financial resources, but this investment reaps even greater rewards. For example, high-throughput genetic sequencing makes it possible to identify new microbes at an unprecedented pace, track outbreaks of antimicrobial resistant bacteria, and probe the functions and dysfunctions of the human microbiome. NIAID's commitment to develop and use innovations such as systems biology approaches, structural biology, sample-sparing assays, the range of scientific "omics," and new imaging and computational technologies ensures that the Institute and its grantees are poised to act as scientific opportunities and public health needs arise.

Research Resources and Infrastructure

NIAID is dedicated to building and sustaining comprehensive domestic and international resources that provide expertise and services throughout the research and product development lifecycle. These resources support scientists worldwide in conducting the highest quality research, by leveraging state-of-the-art technology; accessing critical data and materials through registries and repositories; and establishing and supporting networks of collaborating institutions, Centers of Excellence, and clinical trials networks.

Biodefense and Emerging and Re-emerging Infectious Diseases

Key resources and infrastructure are necessary to facilitate basic research and support the development of new vaccines, therapeutics, and diagnostics for infectious diseases. The availability of state-of-the-art DNA sequencing, bioinformatics, computational tools, and databases, as well as product development services, provides the scientific community with the tools that are critical to better understanding and limiting the impact of these diseases. These services have been instrumental in advancing products for numerous pathogens, including new drugs for influenza and malaria. Future scientific advances require continued development of such critical resources for conducting research on highly infectious pathogens.

PRIORITY 1: Develop and provide resources to facilitate basic and applied infectious disease research. Resources include biological materials, genomic sequencing, bioinformatics, and systems biology tools.

PRIORITY 2: Provide the infectious disease research community with access to a comprehensive suite of preclinical development services that can fill particular knowledge gaps critical to moving products

along the product development pathway, including *in vitro* and *in vivo* assays and animal models of infectious diseases.

PRIORITY 3: Provide the infectious disease research community with access to clinical evaluation services to facilitate clinical trials of vaccines, therapeutics, and other biologics and drugs to prevent and treat infectious diseases.

PRIORITY 4: Conduct outreach efforts to inform the research community of scientific resources readily available to authorized users, clearly delineating information on access and requirements for use. Support mechanisms for sharing data within the scientific community and assess the need for additional services.

HIV/AIDS

NIAID is committed to developing and supporting the research infrastructure and scientific expertise needed to enable innovative approaches to HIV/AIDS research. Toward that end, NIAID has worked to restructure its clinical trials networks to 1) allow for a multi-disease research capacity; 2) focus on targeted scientific opportunities and priorities, including community engagement; and 3) increase flexibility within the network infrastructure to ensure the efficient use of resources. With regard to research resources for HIV/AIDS research, NIAID has the following priorities.

PRIORITY 1: Establish and maintain the robust and flexible resources required to facilitate and advance HIV/AIDS research.

PRIORITY 2: Stimulate and strengthen HIV/AIDS research by:

- Nurturing cross-disciplinary scientific and scholarly opportunities
- Creating research and training opportunities that enable scientists and those in related fields of scholarship to engage in interdisciplinary research, including epidemiology, bioethics, immunology, and infectious diseases, to advance discovery in HIV/AIDS and HIV-associated infections
- Supporting development of a diverse pool of researchers in basic, preclinical, and clinical HIV/AIDS research

PRIORITY 3: Establish and maintain support for product development activities for high-priority vaccine, other prevention, and therapeutic approaches.

PRIORITY 4: Develop and support efficient, flexible, and responsive clinical trial capability and observational cohorts required to translate scientific discoveries into clinical advances and to correlate biologic factors with clinical outcomes.

PRIORITY 5: Foster and support community engagement and education programs to ensure that communities heavily affected by HIV and HIV-associated infections participate in all stages of planning and implementation of HIV/AIDS research.

PRIORITY 6: Take steps to enable and encourage collaborations across public and private sector partners to optimize efficient use of resources, including facilities, expertise, data and data analysis, specimens, reagents, and access to populations.

Infectious and Immunological Diseases

NIAID supports the development of a diverse array of immunologic resources that are available to the scientific community at no or minimal cost. These resources, which include research databases, analytic tools, mathematical models, bioinformatics support, reagents, and animal models, will enable the continued advancement of immunological discovery and its application.

PRIORITY 1: Provide bioinformatics support for NIAID-supported researchers to include optimized methods for data collection, storage, exchange, and interoperability; analytical tools; and data visualization tools.

PRIORITY 2: Support the discovery, validation, development, and standardization of specialized reagents, assays, and technologies that are needed to facilitate basic, preclinical, and clinical research programs in immunology and immune-mediated diseases.

PRIORITY 3: Support the development of animal models for research on immunology and immune-mediated diseases; the housing of widely used rodents and large animals and their distribution to the research community; and breeding and genetic characterization of specialized animal resources, including nonhuman primates.

Research Training and Career Development

Sustaining a broad research program requires support to help investigators develop the knowledge and skills required by changing public health needs and new scientific opportunities. The complexity of contemporary research and the emergence of new fields of study, such as bioinformatics, and of new technologies, increasingly demand that investigators take an integrated, multidisciplinary approach to solving scientific problems. In addition, NIAID is committed to encouraging a diverse research workforce equipped to conduct research in the fields of infectious diseases, allergy, and immunology, including those diseases within the Institute's research portfolio that disproportionately affect underserved populations.

PRIORITY 1: Utilize the full variety of available extramural and intramural award mechanisms to attract and develop the next generation of talented U.S. and international research investigators, including the transition to the first independent academic research appointment and grant. Equip them to engage in interdisciplinary research in immunology and infectious diseases that incorporates state-of-the-art and emerging technologies.

PRIORITY 2: Support extramural and intramural training and career development programs to expand the pool of well-trained U.S. and foreign investigators capable of designing and conducting patient-oriented research. This research includes international clinical trials that ensure the ethical treatment of human subjects and consider social, cultural, and local community concerns.

PRIORITY 3: Provide a broad spectrum of research training and career development opportunities at various educational and career stages to help ensure that diverse pools of highly trained scientists will be available to conduct infectious disease and allergy/immunology research, with an emphasis on the elimination of health disparities.

Communications and Outreach

The full benefit of research through translation into medical practice can be realized only when new knowledge is disseminated, not only to other scientists but also to voluntary and scientific organizations, health care providers, and the general public in the United States and internationally. An important part of the NIAID mission is to disseminate research results to the media, health professionals, and the general public; and to facilitate recruitment of volunteers into clinical trials of candidate vaccines, diagnostics, and therapeutics, and into other clinical research studies.

PRIORITY 1: Promote and sustain interactions with researchers, healthcare professionals, and the general public by: 1) communicating research priorities and results using a range of digital and traditional media tools; and 2) targeting outreach activities via professional and community meetings, workshops, seminars, and conferences.

PRIORITY 2: Maintain effective communication with Congress and other branches of the U.S. government to delineate clearly the role of NIAID in improving public health, both domestically and internationally.

PRIORITY 3: Enhance the recruitment and retention of volunteers into domestic and international clinical research studies through the production and dissemination of culturally appropriate educational materials and outreach to relevant communities, with special attention to those communities most affected by the diseases being addressed.

Global Health Research

"It is imperative that we use our current momentum to move forward, recognizing that the enormous challenges of global health...will require a long-term commitment that is sustained even when global health and those fighting to improve it are no longer in the headlines." —Anthony S. Fauci, M.D.

To comprehensively execute its mission, NIAID must support research on infectious diseases within the populations and in locations where these diseases are prevalent. In addition, the Institute must have the ability to respond rapidly to emerging and re-emerging infectious diseases. In today's interconnected world, health threats that emerge or remain common in distant regions can threaten the health and stability of the United States and other nations around the world. To respond to such threats, it is essential that NIAID support and conduct the best science possible, wherever the scientific opportunities present themselves. HIV/AIDS, tuberculosis, malaria, neglected tropical diseases, and other leading causes of infectious disease affect global health. Accordingly, research on these infectious diseases is best pursued through mutually beneficial partnerships between U.S. scientists and scientists and institutions in countries where these conditions are endemic. NIAID recognizes that global health research must involve shared leadership, a commitment to long-term sustainability, and the engagement of local communities.

NIAID-supported global health research has yielded critically important basic science advances as well as new or improved diagnostics, therapies, and vaccines. NIAID will continue its commitment to well-designed and ethical global health studies, keeping pace with expanding opportunities in infectious disease and immunology research while staying ahead of expanding health threats that loom worldwide.

Area of Emphasis: Develop and maintain international scientific collaborations

La Red is a multi-site collaboration between NIAID and the Mexico Ministry of Health, designed to build capacity and promote sustainability to continue clinically relevant and high-quality research on emerging infectious diseases. La Red's five sites in Mexico City include two sites focused on pediatric research.

Scientific collaborations are integral to the successful achievement of global health research priorities. Research must be performed in regions where diseases and health conditions of interest are endemic. Fostering and supporting international scientific collaborations is critical to the NIAID mission. Despite significant challenges, NIAID has a history of maintaining successful international collaborations while also exploring and pursuing opportunities to expand this effort.

PRIORITY 1: Support and strengthen international basic, applied, and clinical research to advance fundamental discovery and improve the prevention, treatment, and diagnosis of infectious and immune-mediated diseases.

PRIORITY 2: Support and establish targeted research collaborations in countries with emerging economies and a growing commitment to scientific excellence, such as Brazil, China, India, Indonesia, South Africa, and Turkey.

PRIORITY 3: Identify and provide access to research opportunities in regions where scientific collaboration previously has been limited.

PRIORITY 4: Advance opportunities for scientific engagement in regions of strategic importance for biodefense research.

PRIORITY 5: Foster and coordinate trans-NIAID engagement in international collaborations to enhance efficient program integration and cost effectiveness.

Area of Emphasis: Enhance research capacity where scientific opportunities exist

The individuals who conduct, support, and participate in international health research are critical in ensuring the success of studies and sustaining productive research sites. Qualified administrative and research staff with a firm understanding of the fundamental requirements of high-quality health research are essential. Also needed are personnel with clinical research expertise and the capacity to carry out the basic elements of a wide range of studies. To sustain productive research environments it is important to provide training opportunities and mentoring to local researchers to help them advance to leadership roles. In addition, researchers must engage positively with communities, gain the support of political and institutional leadership, and understand local norms and concerns.

NIAID's HIV/AIDS Clinical Trials Networks implement research focused on prevention, treatment, and vaccine development. The Networks have significantly expanded research capacity worldwide through mentorship and scientific engagement. NIAID is building on the success of its current HIV/AIDS Clinical Trials Networks to expand the infrastructure, supporting studies on HIV/AIDS; tuberculosis and hepatitis C, common co-infections in HIV-positive individuals; and antibacterial resistance.

Capable, well-trained administrative staff, research support resources, policies, and procedures must be in place to ensure efficient, effective, and ethical management of sustainable, multi-discipline research sites. Administrators need to develop procedures to accept electronic transmissions of award funds, accounting systems, and computer systems for fiduciary tracking and reporting. Functional Institutional Review Boards or Ethics Review Committees that are qualified to review and monitor a variety of studies in a timely manner are essential to international clinical research. Sites require leadership with strong human resource management skills, with the flexibility to identify and recruit appropriate staff or shift them easily between assignments to address specific research requirements for specific studies.

PRIORITY 1: Invest in scientific activities that help expand research capacity, including laboratories, field sites, scientific and support personnel, and modern research infrastructure such as data repositories.

PRIORITY 2: Develop, maintain and enhance training to increase foreign scientists and institutions' ability to implement high-quality research, comply with NIH administrative and fiduciary requirements,

and manage complex laboratory and field-site challenges, including the safe management of biosafety facilities.

PRIORITY 3: Collaborate with other research support organizations to leverage investments that enhance international research capacity and expertise development.

PRIORITY 4: Utilize networks of U.S. and foreign investigators to expand research capacity by fostering international scientific leadership through mentoring and career partnerships.

Area of Emphasis: Expand international research partnerships and policies

In 1980, the International Collaborations in Infectious Disease Research (ICIDR) program was established to provide funding to U.S. institutions that engage with foreign institutions in tropical medicine and emerging infectious diseases research. ICIDR establishes a relationship between foreign (non-U.S.) and U.S. institutions to support the study of infectious diseases of global health importance, particularly in resource-constrained countries. Through these collaborations, investigators increase scientific knowledge, promote research capacity, and enhance the international research experience of all the involved investigators.

Through its global health investment, NIAID has had an impact on research policy and practice, often working in partnership with others. Establishing and maintaining partnerships within the Department of Health and Human Services (HHS), with other U.S. government agencies and their counterparts in other countries, and with many nongovernmental organizations helps NIAID accomplish its legislative mandate and enhance and expand its global research activities. In recent years, NIAID has enhanced its collaborations with other NIH Institutes and Centers that share a global research interest. Other key partnerships include the Centers for Disease Control and Prevention (CDC), the Department of Defense, and large philanthropic organizations such as the Bill &

Melinda Gates Foundation and the Wellcome Trust. In developing partnerships, NIAID collaborates with organizations that have a shared vision and can complement NIAID's investments to advance global health research.

PRIORITY 1: Form strategic partnerships with U.S. government agencies, other governments' biomedical research funding entities, multilateral organizations, and civil society/nongovernmental groups.

PRIORITY 2: Assign NIAID scientists and science administrators in countries of key scientific interest, including China, India, Mali, South Africa, and Uganda.

PRIORITY 3: Foster health and science diplomacy by facilitating the exchange of scientists and the engagement of NIAID leadership in global health research activities and interactions.

PRIORITY 4: Assure the representation of NIAID priorities in senior-level U.S. delegations to countries or regions of scientific interest.

PRIORITY 5: Negotiate and enter international agreements to advance NIAID's global health agenda.

PRIORITY 6: Ensure integration of the NIAID research objectives into the U.S. government's global health programs and priorities.

PRIORITY 7: Disseminate scientific knowledge and study findings to facilitate global utilization of research results and enhance evidence-based biomedical and public health practice.

Principles for Global Health Research

NIAID implements all of its international activities in keeping with four core principles, which also are reflected in the HHS Global Health Strategy.

1. Research should reflect the highest possible scientific standards.

NIAID-supported global research reflects the scientific mission, strategic priorities, and research agendas of the Institute and of the collaborating institutions. All NIAID-supported research should be based on the best-available, current scientific knowledge, including appropriate epidemiology, and adhere to the highest standards of scientific quality and integrity. To conduct the highest quality research with the greatest scientific impact, researchers must be prepared to work collaboratively in regions where diseases and health conditions of interest are endemic.

2. Research should adhere to the highest possible ethical and regulatory standards.

Investigators and institutions conducting global health research must adhere to the highest ethical and regulatory standards for the oversight of research, as established and recognized by international, host country, and U.S. ethics committees. Research should take place within a framework developed to assure the equitable and fair sharing of intellectual property and materials, using transfer agreements that are consistent with legal and ethical standards and scientific needs. Global health research should always reflect an awareness of, respect for, and responsiveness to diverse contextual and cultural realities and perspectives.

3. Research should reflect shared interests and international and local public health needs and priorities.

Global health research should be based on shared scientific interests and mutually agreed-on priorities. In community-based clinical studies, local communities should be involved, to the greatest degree possible, in research planning and implementation, and in the dissemination of study findings to local stakeholders. In undertaking international research the investigators and NIAID should assure that the studies have been designed and conducted with local public health needs and priorities in mind.

4. Research should involve mutually advantageous collaborations with institutions and communities of the host country and other partners.

U.S. investigators should establish and maintain respectful, mutually beneficial collaborations and partnerships with host country scientists and institutions, local partners, funders, and other organizations. All stakeholders should be substantively engaged in the joint planning, development, and dissemination of research findings, including arrangements for the transfer and sharing of technology and knowledge.

Current and Future Global Health Research

The principles, priorities, and strategies presented here are embedded within the programs and activities of NIAID's intramural and extramural divisions. Although NIAID is a long-recognized leader in global health research, its programs and approaches to this research continue to evolve in response to both challenges and emerging opportunities. Global research requires a significant investment in funding, time, dedication, and a commitment to long-term engagement. Through its programmatic divisions, NIAID conducts basic research, supports networks of U.S. and international scientists, trains U.S. and foreign investigators to work internationally, and enhances research facilities around the world. NIAID's commitment to international research is reflected in the actions of its director, the Institute's strategic priorities, and the programs implemented by the Divisions as they pursue scientific opportunities throughout the world to improve the health of Americans and of individuals worldwide.