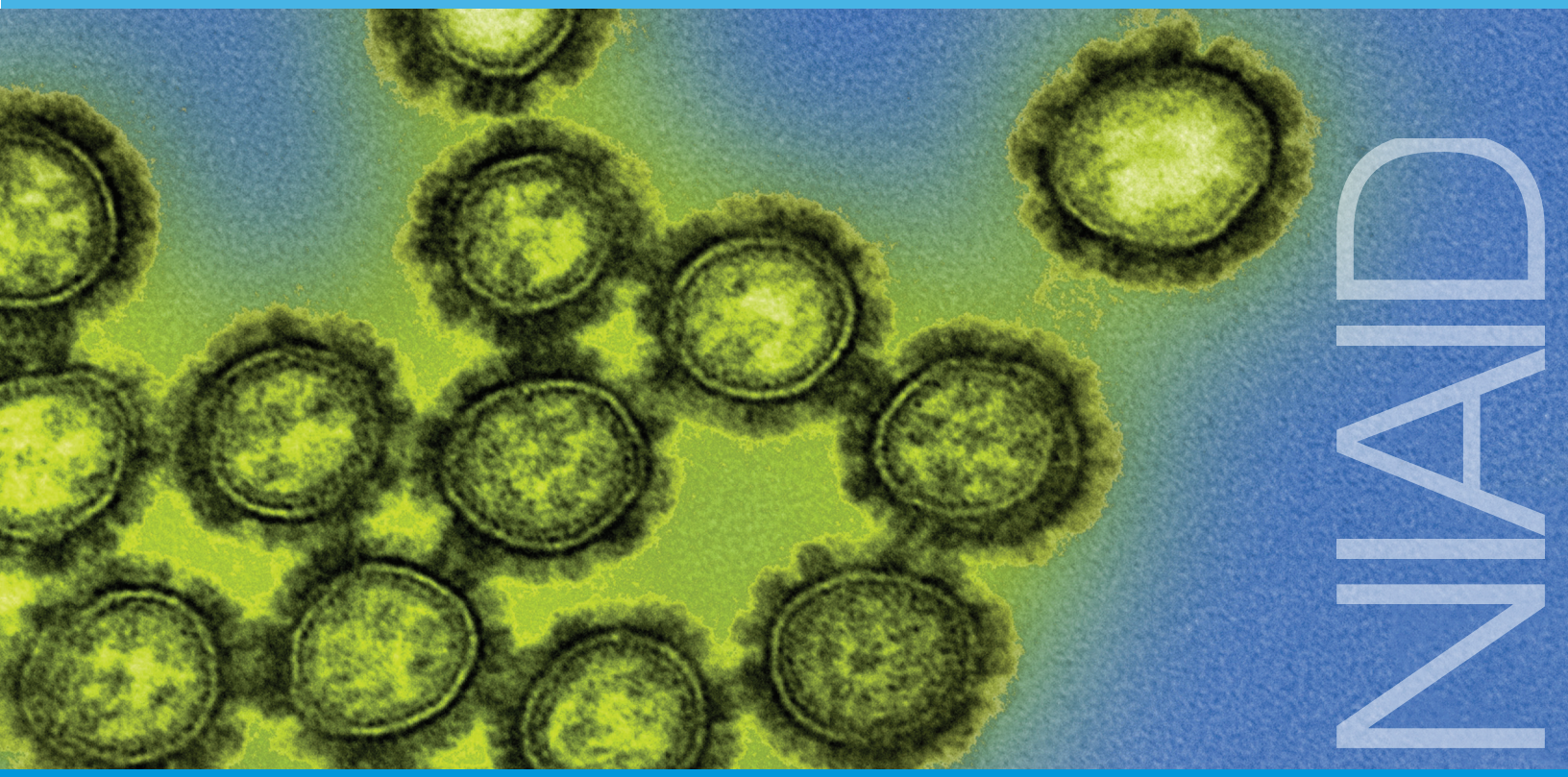
NIAID Strategic Plan 2017



National Institute of Allergy and Infectious Diseases

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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 due to infectious and immune-mediated diseases 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: (1) Infectious Diseases (non-AIDS), Including Emerging and Re-emerging Diseases and Biodefense; (2) HIV/AIDS; (3) Allergy, Immunology, and Immune-Mediated Diseases; and (4) 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. Over the years, we have witnessed dozens of such threats to public health, such as 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 novel pathogenic coronaviruses, the increasing spread of dengue fever, and the development of multidrug-resistant bacteria and extensively drug-resistant tuberculosis. More recently, the serious outbreak of Ebola virus infections in West Africa led to a rapid NIAID response based on years of prior research developing possible countermeasures for this and other potential emerging pathogens. Finally, the outbreak of Zika virus in the Western hemisphere, with its associated birth defects, has also been met by a rapid NIAID response to develop medical countermeasures.

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. 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 2017 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 2017 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 both domestic and 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 HIV/AIDS, tuberculosis (TB), and malaria; emerging or re-emerging threats such as influenza, antibiotic-resistant bacteria, and multidrug-resistant TB (MDR TB); 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 to respond to emerging or re-emerging infectious disease 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 diagnostics, therapeutics, and vaccines to prevent and treat the many infectious, immune-mediated, and allergic diseases that afflict people in the United States and 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. Several products in each of these categories are now in the Strategic National Stockpile, a repository of life-saving pharmaceuticals and medical supplies that may be dispensed to protect the American public in the event of a public health emergency. Because new, potentially deadly pathogens, such as avian influenza, could occur naturally or be deliberately introduced by terrorists, NIAID biodefense research is integrated into its larger emerging and re-emerging infectious diseases portfolio. Indeed, during each outbreak of either a newly emerging disease (e.g., Middle East respiratory syndrome coronavirus, or MERS-CoV) or the novel presentation of an existing disease (as was the case with Ebola in West Africa, enterovirus D68 in the United States, and Zika in the Western hemisphere), NIAID is continually learning more about infectious diseases and incorporating those lessons into ongoing research programs, ensuring that we are prepared to address a wide range of infectious disease threats.

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 new diagnostics, therapeutics, and vaccines. 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 TB and hepatitis C, common co-infections in HIV-infected people. In addition, the Institute has established a clinical research network to address antibiotic-resistant bacteria, 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, and malaria, 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 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-supported 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 in 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 more than 60 years, NIAID research has led to new diagnostics, therapeutics, vaccines, 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 2015, three of the ten leading causes of death in the world were infectious diseases.[1] Of the 5.9 million deaths in children under five that occurred in 2015, about half were caused by infectious diseases and conditions such as pneumonia, diarrhea, malaria, meningitis, tetanus, HIV and measles.[2]

New challenges arise continually, including the emergence of antibacterial resistance as a major public health issue. Both hospital-acquired infections, such as *Klebsiella pneumoniae*, and community-acquired infections, such as urinary tract infections, are becoming more difficult to treat as drug resistance increases. Some drug-resistant bacteria, such as certain strains of *Neisseria gonorrhoeae*, are no longer responsive to any traditional treatments. Research on new therapeutics to treat these infections and new diagnostics to detect drug-resistant pathogens is an essential part of addressing this growing problem.

While we know that some microbes can cause significant health issues, we also are learning that interactions between humans and microbes can be quite complex. In the last several years, NIAID has expanded efforts to study the microbiome (the microbial communities that live in and on the human body), to better understand how microbes interact in the context of their environment and the roles they play in health and disease.

Natural genetic variations also allow novel strains of known pathogens to appear, such as the new strain of H1N1 influenza A that caused a pandemic in 2009. NIAID support for influenza research over the past several years has greatly improved our preparedness for and ability to respond to subsequent events, such as the 2013 and current H7N9 influenza A outbreaks. Through this research, we have learned that continued vigilance, planning, and strong biomedical research capability and public health response are essential defenses against emerging health threats.

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[1] The World Health Organization [Internet]. The top 10 causes of death. Geneva: World Health Organization [updated 2017 Jan; cited 2017 April 17]. Available from: www.who.int/mediacentre/factsheets/fs310/en/index2.html.
[2] You, Danzhen *et al.* Levels & Trends in Child Mortality: Report 2015.New York: United Nations Children's Fund; 2015.

Despite advances, many infectious diseases are not adequately controlled. Some pathogens, such as the parasite that causes malaria, continue to cause significant morbidity and mortality internationally. In addition, the resurgence of some diseases, such as TB, resulted from evolution of pathogen strains that are highly resistant to available treatments. Currently, multidrug-resistant TB (MDR TB) and extensively drug-resistant TB (XDR TB) are major health threats globally. Neglected tropical diseases (NTDs), such as 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. (For more information on global health research, please see the section on Global Health Research.)

More than 17 percent of infectious diseases, including some of those previously mentioned, are transmitted by vectors such as mosquitoes, sand flies, ticks, or freshwater snails. Recent outbreaks of mosquito-transmitted viruses, such as dengue, chikungunya, and Zika, in the United States and the Americas attest to the importance of maintaining a foundation of research on the vectors themselves, vector-host and pathogen-vector interactions, vector ecology and genomics, and insecticide resistance. NIAID supports research to identify potential targets that could inform development of novel vector control methods, such as larvicides, insecticides, and repellents. For instance, NIAID is evaluating the effectiveness of larvicide-treated male mosquitoes and a biopesticide approach in reducing mosquito populations.

NIAID plays a key role in the national strategy to develop medical products and approaches to counter bioterrorism and emerging and re-emerging infectious diseases. As the largest Ebola epidemic in history spread throughout West Africa in 2014–2015, the importance of NIAID research on emerging and re-emerging infectious diseases was brought to light. NIAID-funded investigators were prepared to use advanced genomic technologies to sequence the Ebola virus genomes from clinical isolates obtained from Ebola patients and to accelerate ongoing research on therapeutics, vaccines, and diagnostics. Research investments by NIAID in biodefense and emerging and re-emerging infectious diseases paved the way for this rapid response to a dangerous infectious disease outbreak.

The development and testing of successful therapies, diagnostics, and prevention technologies relies on partnerships. 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. NIAID has supported the Partnerships Program since 2002 to foster early product development research and ultimately increase the number of new products for the prevention, treatment, and diagnosis of emerging and re-emerging biological threats. This program has helped to ensure that promising basic research findings and technologies are translated rapidly into new approaches for product development. Moreover, it has encouraged many new research collaborations between experts from different disciplines of academia and industry, and as a result has helped to expand the pool of scientists addressing public health threats.

To date, this interactive program has supported hundreds of early and mid-stage translational research projects. Several candidate products have advanced sufficiently to gain HHS support for advanced development (e.g., multiple anthrax and Ebola countermeasures, a novel influenza therapeutic, an immunostimulatory patch, a cell culture-derived influenza vaccine, and several diagnostic devices). In

addition, Partnerships projects have yielded several FDA-cleared, commercially available diagnostic devices for influenza, TB, and other respiratory diseases, as well as gastrointestinal diseases and sepsis.

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, the NIAID International Centers of Excellence for Malaria Research (ICEMR) program uses a multidisciplinary approach that aims to identify the current obstacles to malaria control, and the basic science questions that need to be resolved in order to eliminate these obstacles. It is expected that such studies will provide the knowledge base necessary for improved clinical and field management of malaria, as well as guide the development of new tools and interventions.

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; response to therapeutics; 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. For example, NIAID-funded researchers are using a comprehensive systems biology approach to identify the network of interactions of multiple *Mycobacterium tuberculosis* (Mtb) transcription factors—genetic regulators that determine how Mtb survives and reacts to its environment—to unveil the blueprint of how Mtb switches between different stages of infection and disease. This blueprint is also being used to determine how Mtb responds to different drugs, and may help identify more effective treatment combinations. With this framework, researchers may be able to develop appropriate therapies for each stage of the disease. 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: Translational research – 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. Moreover, NIAID supports 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.

Diagnostics

As infectious diseases continue to take their toll around the world, an urgent need exists 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. For example, to enable physicians to make more informed treatment decisions in Lyme-endemic areas, NIAID supports the development of new diagnostic tools for Lyme disease. Additionally, the introduction of the Xpert® MTB/RIF (Cepheid) test for diagnosing TB, developed in part through NIAID support, addressed the urgent need for new tools to rapidly diagnose TB and its drug-resistant forms. The Xpert test now forms the platform for diagnostics for a number of healthcare-associated infections, sexually transmitted infections, and influenza. In the midst of the West African Ebola epidemic, FDA approved an Emergency Use Authorization (EUA) for Xpert as an Ebola diagnostic—demonstrating the value of the NIAID strategy of investing in platform technologies that can be rapidly adapted for emerging and re-emerging diseases.

In addition, NIAID supports research to develop multiplex platforms capable of detecting multiple pathogens and/or toxins in a single test. The multiplex diagnostic platform FilmArray® (Biofire), developed with NIAID support and approved by the FDA, can detect multiple respiratory pathogens from patient samples and differentiate among particular influenza strains. FilmArray has now increased capacity to include FDA-approved gastrointestinal and blood culture panels. NIAID helped support the development of a biothreat panel, and an EUA was granted for Biofire's Ebola diagnostic during the recent epidemic. NIAID is also advancing development of other types of diagnostics, including those using novel technologies such as microfluidics, optofluidics, and nanophotonics, which are capable of detecting an array of viruses, including Ebola. 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 research, including using advanced genomic technologies, to discover unique characteristics that could be used as specific and sensitive targets to diagnose 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, yellow fever, and influenza. Many of these trials are conducted through longstanding NIAID Vaccine and Treatment Evaluation Units (VTEUs). NIAID has expanded 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, in the face of the recent West African Ebola epidemic, NIAID accelerated the development and testing of multiple Ebola vaccine candidates at various stages in the product development pipeline. In addition, in response to the Zika virus outbreak in the Americas, NIAID moved quickly to support the development of several Zika virus vaccine candidates. Two of these candidates are already being evaluated in Phase 1 clinical trials. NIAID is also committed to advancing the development and evaluation of a number of candidate vaccines to address the ongoing chikungunya epidemic, which poses a new threat to the Western Hemisphere and possibly to the United States; one of these candidates will be tested in an upcoming Phase 1 clinical trial. As new pathogens and novel strains of existing pathogens emerge, including antimicrobial-resistant strains, new vaccines are needed, and NIAID will continue responding to this challenge through vaccine research. In addition to furthering the development of vaccines against specific pathogens, NIAID supports the development of plug-and-play technologies that may improve preparedness capabilities, as well as approaches to medical countermeasure development and manufacturing against multiple threats. These platform technologies increase the response to and development of vaccines against emerging infectious diseases.

Finally, an integral part of the emerging infectious disease challenge is the quest to better understand innate and adaptive immune responses and advance the development of cross-protective vaccine strategies. NIAID funding for projects focused on developing a universal influenza vaccine illustrates the commitment to such cutting-edge vaccine research.

PRIORITY 1: Conduct research to better understand and enhance immune responses, and to identify promising new vaccine targets for TB and other 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 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 some bacterial infections that are increasingly resistant to available antibiotic drugs. To that end, NIAID continues to make antibacterial research a key priority. In response to a 2014 Executive Order outlining federal actions to combat the rise of antibiotic-resistant bacteria, NIAID continues to strengthen and expand its antibacterial resistance research program and reports on these activities in the *National Action Plan for Combating Antibiotic-Resistant Bacteria*. Similarly, NIAID has a key role in responding to the recently established *National Action Plan for Combating Multidrug-Resistant Tuberculosis*, which outlines domestic and global activities to address the rise of MDR TB.

NIAID is supporting efforts to identify new antibiotic classes and products; screen existing products for activity against different pathogens; and combine new or existing compounds to treat drug-resistant infections through intramural research, investigator-initiated research efforts, and dedicated research programs such as the NIAID Antibacterial Resistance Leadership Group (ARLG), a clinical research network established in 2013. NIAID supports multiple clinical trials designed to provide vital information on the optimal use of currently available antibacterial drugs. For example, the VTEUs, in collaboration with the ARLG, recently launched a clinical trial that will evaluate whether a shorter course of antibiotics is effective at treating community-acquired pneumonia in children. The goal of these efforts is to find treatment regimens that limit the emergence of drug resistance. Identifying and approving new uses for existing antimicrobials will provide additional treatment options for patients and facilitate an effective response in the event of a public health emergency. In the area of biodefense, NIAID-supported animal model studies played a major role in the FDA decision to approve licensed products levofloxacin and ciprofloxacin to treat pneumonic plague. Such medications can be stored in the Strategic National Stockpile.

In its 2014 report, *NIAID's Antibacterial Research Program: Current Status and Future Directions,* NIAID outlined a number of new approaches to address bacterial resistance, which are actively under investigation through a number of targeted NIAID research initiatives:

- Systems Biology and Antibacterial Resistance: New Directions for Drug Discovery—Using a holistic approach to examine molecular networks of host-pathogen interactions and global changes in response to drug exposure

- Harnessing the Immune System to Combat Bacterial Infections—Enhancing host immune response through immunological interventions and immunotherapeutics
- Exploring Anti-Virulence Strategies—Targeting bacterial virulence factors without directly killing bacteria to help limit selective pressure
- Synthetic Microbiota: An Ecobiological Approach—Designing microbial communities as biologic products to mitigate infectious diseases and their sequelae
- Diagnostics to Guide Use of Narrow-Spectrum Therapeutics—Decreasing selective pressure by enabling the use of therapeutics targeted to a pathogen or group of pathogens
- Exploiting Natural Predators: the Specificity of Phage Therapy—Using phage or phage-derived lysins to kill specific bacteria while preserving microbiota
- Extending the Clinical Utility of Antibacterial Drugs—Optimizing use of existing drugs and combination therapies to suppress emergence of resistance and minimize toxicity

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.

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 35 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). The discovery, development, and delivery of HAART to millions of HIV-infected people has transformed HIV/AIDS from a death sentence into a manageable disease. These potent antiretroviral drugs (ARVs) have also been shown to be very effective in preventing transmission of HIV and have nearly eliminated mother-to-child transmission (MTCT) of HIV in many parts of the developed world. Results from the NIAID-funded Promoting Maternal and Infant Survival Everywhere (PROMISE) study demonstrated that providing either HAART to mothers or nevirapine to infants during breastfeeding resulted in HIV transmission rates between 0.3 and 0.6 percent from 6 months to 1 year of age. These results provide a roadmap to ending perinatally transmitted HIV infection.

In addition, results of the landmark study known as HPTN 052[3] demonstrated that effective HAART, as defined by no detectable viral load, durably prevents sexual transmission of HIV in adults. Further studies have demonstrated that this powerful effect applies to all modes of sexual transmission. Moreover, the NIAID-funded Strategic Timing of AntiRetroviral Treatment (START) trial demonstrated that immediate treatment with antiretroviral therapy (ART) not only prevents serious AIDS-related diseases but also prevents the onset of cancer, cardiovascular disease, and other non-AIDS–related diseases and deaths. The interim results were so significant—a 57 percent decrease in disease and death—that all participants were informed of the findings and those participants not on ART were offered immediate treatment. These results support findings previously reported from the Strategies for Management of AntiRetroviral Therapy (SMART) study, which showed that the benefits of therapy far outweighed concerns regarding drug toxicity. Overall, these studies conclusively show that early initiation of ART is highly beneficial for the individual as well as for the public health of the community.

To build on these successes, scientists continue to develop new tools and strategies aimed at controlling and ultimately ending the HIV/AIDS pandemic. Toward this end, NIAID continues to expand research to discover a cure for HIV and/or strategies that lead to sustained or lifelong remission in the absence of therapy, as well as other biomedical strategies to prevent acquisition of HIV. Transformative successes in

[3] Cohen MS *et al.* Antiretroviral therapy for the prevention of HIV-1 transmission. *N Engl J Med.* 2016 Sep 1;375(9):830-9.

HIV prevention will likely 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, although in 2009, the RV144 Thai trial provided the first evidence that an HIV vaccine may be possible. Researchers are now building on these results and following two distinct paths of vaccine research, which include evaluating a modified version of the RV144 vaccine regimen and developing strategies to elicit potent broadly neutralizing antibodies. Additionally, new biomedical prevention tools are being evaluated that eliminate the need for high levels of adherence to a daily regimen of pre-exposure prophylaxis (PrEP).

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 is designed to develop and support the infrastructure and biomedical research needed to:

- Reduce HIV incidence through the development of safe and effective vaccines and biomedical prevention strategies that are also highly desirable
- Develop novel treatments for HIV infection and approaches for sustained remission in the absence of therapy
- Define treatment and prevention strategies for the co-infections and co-morbidities of greatest significance
- Foster partnerships to determine how best to implement effective interventions at scale to maximize impact

Area of Emphasis: Reduce HIV incidence through the development of safe and effective vaccines and biomedical prevention strategies that are also highly desirable

The most compelling goal in HIV research is the prevention of HIV infection. The development of a safe, effective, and durable vaccine that can be used in combination with other prevention modalities is the best long-term hope for ending the AIDS pandemic.

Scientists are now working to confirm and extend the results of the RV144 Thai trial, the first clinical HIV vaccine trial to demonstrate modest efficacy in preventing HIV acquisition. The correlates of risk identified from that study may be useful for building a more durable response in future studies being conducted by the Pox-Protein Public-Private Partnership (P5). HVTN 100, the first study conducted in collaboration with the P5, evaluated an HIV vaccine regimen designed to improve on the efficacy of the RV144 regimen, and the modified Pox-prime, protein boost regimen was shown to meet all the criteria to move forward into a test-of-concept HIV vaccine trial. In 2016, NIAID launched HVTN 702, a Phase 2b/3 clinical trial to evaluate the efficacy of the new vaccine regimen.

NIAID is also pioneering strategies to stimulate production of broadly neutralizing antibodies (bNAbs) that have been shown to neutralize a wide range of HIV strains in cell culture. Important areas of

research include identifying where and how bNAbs bind to HIV envelope glycoprotein. To develop strategies to reproducibly induce the production of bNAbs via immunization, the steps in the natural evolution of these antibodies, and viral species that are triggering these responses, are being defined. Importantly, scientists are busy elucidating the three-dimensional structure of the antibodies and the immunogens along these pathways. This work should coalesce into the evaluation of a series of immunogens that will be evaluated for their ability to reproducibly trigger responses that lead to the production of these bNAbs. Passive infusions of bNAbs have been effective in preventing infection in mouse and rhesus macaque models of HIV infection. NIAID is now leading two multinational clinical trials to test the safety and effectiveness in humans of an investigational anti-HIV bNAb called VRC01 for preventing HIV infection. Results of these studies will provide crucial data toward answering the question of what concentration of antibody is required for protection and whether vaccination can trigger a protective immune response.

In the absence of a preventive vaccine, building a number of effective prevention strategies is critical to the fight against HIV/AIDS. Proven prevention methods already exist, such as proper use of condoms, needle exchange, adult male circumcision, PrEP, and treatment as prevention (TasP). However, there are still challenges associated with several of these strategies, including drug adherence and viral resistance. To address these issues, scientists are evaluating new agents, sustained-release products, drug combinations, and delivery methods such as vaginal rings or injectable ARVs; determining the impact of different dosing regimens; and determining the impact of PrEP on specific populations and at a population level. The recently completed ASPIRE study (A Study to Prevent Infection with a Ring for Extended Use) determined that a monthly-use vaginal ring containing the ARV dapivirine (released over a 30-day period) was safe and 27 percent effective for protecting women against HIV infection. Further analysis has shown that for those who used the ring most consistently, the reduction in HIV infection was estimated to be as much as 75 percent or higher. The HIV Open-label Prevention Extension (HOPE) study, an open-label extension trial of ASPIRE, is currently evaluating the prospects for improving adherence.

In addition, the HPTN has completed Phase 2 studies evaluating two investigational sustained-release PrEP products (cabotegravir and long-acting rilpivirine) administered via injection. The results from these studies determined that both drugs were safe and that cabotegravir provided drug concentration levels in both men and women comparable with drug administration once every 8 weeks. Efficacy studies of cabotegravir in men and women are currently underway or planned (HPTN 083 and HPTN 084, respectively).

HPTN 052 previously demonstrated that TasP can eliminate HIV transmission in discordant couples where the HIV-infected partner is durably suppressed. Results from HPTN 052 and other studies now provide convincing evidence that TasP is a powerful public health intervention, provided the target population achieves sustained virologic suppression. Additional protection from HIV acquisition with PrEP will augment the impact of TasP. To define how best to implement TasP, a series of implementation trials are underway in collaboration with the President's Emergency Plan for AIDS Research (PEPFAR). For example, the Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) study is assessing whether house-to-house voluntary HIV testing and prompt

treatment of HIV infection, along with other proven HIV prevention measures, can substantially reduce the number of new HIV infections across communities in South Africa and Zambia. A second study, the Sustainable East Africa Research in Community Health (SEARCH) study, is evaluating mass community HIV testing and early initiation of ART in Uganda and Kenya. The purpose of these studies is to define whether these strategies, which are focused on the UNAIDS 90-90-90 targets of achieving 90 percent of all people living with HIV to be diagnosed, on treatment, and virally suppressed, can reduce the rates of HIV transmission below the level required to sustain the pandemic.

PRIORITY 1: Establish pathways for rational development of effective HIV prevention modalities that provide protection against all routes of HIV exposure, and reduce the impact of poor adherence on efficacy.

PRIORITY 2: Drive research to discover safe and effective vaccine candidates, including:

- Establishing and supporting the infrastructure for the manufacturing and testing of novel immunogens and broadly neutralizing antibodies
- Identifying and characterizing vulnerable viral epitopes, developing and evaluating immunogens that induce broadly neutralizing antibodies, defining better methods of antigen presentation, and testing protective efficacy of broadly neutralizing antibodies identified through structure-driven immune design
- Developing strategies to optimize the evaluation of B-cell responses

PRIORITY 3: 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, e.g., complete the HVTN 702 clinical trial in South Africa, which builds on the results of the Thai trial
- Expediting the clinical evaluation and sequential use of potent immunogens
- Efficiently using molecular tools to assess the vaccine effect
- Rapidly assessing potential correlates of immunogenicity and of protection elicited by experimental vaccines
- With partners, producing a vaccine that is effective for various risk groups and demographics and protects against different modes of transmission

PRIORITY 4: Evaluate and improve acceptability and behavioral adherence for PrEP, microbicides, and broadly neutralizing antibodies.

PRIORITY 5: Evaluate the effectiveness of improved PrEP and microbicide products, such as sustained release agents, in the most at-risk populations.

PRIORITY 6: Advance a comprehensive biomedical research program that incorporates appropriate behavioral factors to develop and evaluate safe, effective, and acceptable non-vaccine prevention methods and optimal formulations, dosages, and product delivery methods.

PRIORITY 7: Establish partnerships to devise, test, and determine the best way to implement proven prevention interventions for specific settings and populations.

Area of Emphasis: Develop novel treatments for HIV infection and approaches for sustained remission in the absence of therapy

The greatest achievement in HIV research has been the discovery, development, and delivery of ART to millions of HIV-infected people, leading to a life expectancy similar to uninfected individuals. Treatment can block further disease progression, preserve remaining immune function, and more recently has been shown to prevent HIV transmission. This latest 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 HIV-positive people alike. Continuing to improve the safety and durability of therapeutic regimens will also enhance the treatment and prevention effects of ART. In addition, NIAID supports basic research regarding the development of novel approaches to eliminate HIV from the body.

Despite these huge advances, treatment for HIV/AIDS requires lifelong drug therapy, which can lead to issues with adherence, cumulative drug toxicities, and the development of drug resistance. Sustained-release products for treatment are currently being evaluated and could have a significant impact on the management of HIV and outcomes of treated HIV disease. While ART can be extremely effective in suppressing detectable viral replication for extended periods, no documented cases of a spontaneous cure have occurred in the 30-plus years of the HIV epidemic. One HIV-infected individual, referred to as the "Berlin Patient," has been "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 strains. 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 eliminated from the body.

Given the challenges inherent to lifelong ART, there is an increased interest in developing a cure for HIV. 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) complete suppression of the virus in the absence of therapy—i.e., a functional cure. A cure for HIV infection must be safe, scalable, and less traumatic to patients than current treatment regimens and will most likely require a combination of approaches. Current areas of research are focusing on understanding the fundamental nature of viral latency and persistence, translational research into the discovery and development of novel strategies (e.g., broadly neutralizing and modified antibodies as well as novel delivery strategies), discovery of assays and robust biomarkers, clinical research into interventions capable of achieving eradication or sustained remission of HIV, and behavioral and social science research that informs the development, testing, and implementation of HIV cure interventions.

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

- Determining the nature and distribution of reservoirs of HIV infection within the human body
- Defining the processes that govern reservoir establishment and maintenance
- Understanding the mechanisms of persistence in persons receiving effective ART

PRIORITY 2: Discover and evaluate novel interventions, sustained-release formulations, and drug delivery technologies to diagnose and treat HIV, leading to significant, durable improvements in therapy and treatment outcomes.

PRIORITY 3: Develop methods to simply and accurately measure the reservoir as well as predict and detect virologic rebound in HIV-infected persons.

PRIORITY 4: Identify and clinically evaluate novel concepts or strategies that target, create immunity, and eliminate viral reservoirs resulting in a functional or sterilizing cure.

Area of Emphasis: Define treatment and prevention strategies for the co-infections and co-morbidities of greatest significance

HIV-associated co-infections are potentially life-threatening conditions caused by a wide range of microorganisms, including protozoa, viruses, fungi, and bacteria. In addition, co-infections such as TB, hepatitis C (HCV), and hepatitis B (HBV) complicate the medical management of HIV-infected people and result in significant morbidity and mortality, especially in resource-limited settings. Consistent with its commitment to improving disease outcomes, NIAID supports programs to advance understanding, prevention, and treatment of these major co-infections.

HIV infection is a risk factor for conversion of latent TB infection to active TB (reactivation), 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. Current research is focusing on optimizing treatment of TB and developing strategies to address TB reactivation in HIV-infected individuals. Additional areas of research include evaluating new anti-TB drugs and drug combinations, developing shorter treatment regimens, treating MDR/XDR TB, and preventing TB infection. With regard to HCV, a major success has been the demonstration that the direct acting antivirals to treat HCV are nearly 100 percent curative in dually infected people. Due to the effectiveness of new HCV therapy, the focus is now shifting to research on HBV in the context of HIV infection.

With safe and effective ART beginning in the early 2000s, HIV-infected individuals are living longer, with an estimated life expectancy similar to that of the general population. As a result of this longer survival, almost 25 percent of all people infected with HIV in the United States are 50 years old or older; data suggest that within the next few years, this age group will comprise almost 50 percent. These individuals face unique challenges due to HIV infection and long-term use of ART, such as chronic immune activation, malignancies, kidney disease, or cardiovascular disease (CVD). For instance, studies have shown that HIV-infected individuals are at a higher risk (1.5–2 times) of developing CVD. This higher risk may be linked to the consequences of the chronic immune activation and inflammation that persist in HIV-infected individuals on ART, which may contribute to metabolic disorders such as lipodystrophy, atherosclerosis, and subsequent cardiovascular events, such as heart attacks. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study, led by the National Heart, Lung, and Blood Institute (NHLBI), was launched in 2015 to explore the effect of a cholesterol-lowering statin drug on preventing heart disease in HIV-infected people.

PRIORITY 1: Elucidate the pathogenic mechanisms and consequences of TB and other high-priority co-infections in the context of HIV infection. This includes defining mechanisms of TB acquisition and reactivation.

PRIORITY 2: Develop improved diagnostics and prognostic biomarkers for TB in all age groups.

PRIORITY 3: Develop and test new drug and vaccine strategies for the prevention and/or suppression of reactivation of all forms of TB in the context of HIV infection.

PRIORITY 4: Enhance understanding of the mechanisms of chronic immune activation and associated co-morbidities, develop and evaluate potential therapies to eliminate or suppress immune activation and associated clinical consequences, and explore the role of HIV in the development of premature aging of the immune system in HIV-infected individuals on suppressive ART.

PRIORITY 5: Define long-term consequences of treated HIV infection and the mechanisms of morbidity associated with treated HIV disease. Partner with experts on prominent end-organ diseases to evaluate prevention and treatment approaches.

PRIORITY 6: Support research for infectious hepatitis as an HIV-associated infection by:

- Optimizing effective drugs that cure HBV in patients co-infected with HIV
- Developing improved diagnostics, noninvasive indicators of liver injury, and prognostic biomarkers for treatment outcomes
- Identifying pathways and mechanisms that accelerate the course of HBV disease in HIV co-infected individuals

PRIORITY 7: Support clinical studies of other high-priority co-infections to improve diagnostic, treatment, and prevention strategies.

Area of Emphasis: Foster partnerships to determine how best to implement effective interventions at scale to maximize impact

The establishment of proof of concept for new 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. Examples of ongoing collaborations in priority areas of research are described below.

Prevention

NIAID collaborates with foundations, private industry, other NIH institutes and federal agencies, foreign governments, and other organizations to conduct relevant clinical research and evaluation of candidate HIV vaccines worldwide. A prominent example is the P5, 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 are NIAID, the Military HIV Research Program (MHRP), the Bill & Melinda Gates Foundation (BMGF), the HIV Vaccine Trials Network (HVTN), Sanofi Pasteur, GlaxoSmithKline (GSK), and Eurovacc. Through this collaboration, NIAID has launched two important studies (HVTN 100 and HVTN 702) to evaluate an investigational HIV vaccine regimen that was designed to improve upon the efficacy of the RV144 regimen.

More recently, NIAID, in collaboration with Crucell/Janssen (a Johnson & Johnson company), the Ragon Institute, the Beth Israel Deaconess Medical Center, and the MHRP, initiated the first Phase 1 trial to evaluate the safety and immunogenicity of Ad26, MVA, trimeric HIV envelope protein mosaic vaccines. A Phase 2b study is currently in development and scheduled to begin in 2018. This collaboration will also include planning for efficacy evaluation of the lead heterologous prime-boost candidates from these early studies. In addition, Phase 1/2 studies are in development to evaluate new products and regimen optimization.

Another prime example of partnerships is the PopART study. This study is sponsored by NIAID, being conducted by the NIH-funded HIV Prevention Trials Network (HPTN), and funded primarily by PEPFAR. Additional funding is provided by the International Initiative for Impact Evaluation with support from BMGF, as well as by NIAID, the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). Partners of PEPFAR are providing HIV care and treatment to the study communities under the direction of the U.S. Agency for International Development (USAID) and the U.S. Centers for Disease Control and Prevention (CDC). The study is being led by investigators at the London School of Hygiene and Tropical Medicine, in collaboration with Imperial College London, the Zambia AIDS Related Tuberculosis Project, and the Desmond Tutu TB Centre at Stellenbosch University, South Africa. NIAID also is supporting the SEARCH study in collaboration with the U.S. Office of Global AIDS Coordinator.

Treatment and Cure

NIAID collaborates with other NIH institutes and centers, including the National Cancer Institute, NHLBI, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NIDA, the National Institute of Neurological Disorders and Stroke (NINDS), and NIMH. For example, NIAID co-funds the NIMH-led study Eradication of HIV from CNS Reservoirs: Implications for Therapeutics Program, which supports 14 clinical studies aiming to address HIV persistence in the central nervous system (CNS) of HIV-infected people on treatment, including a large project to develop interventions to reduce the latent CNS reservoir during acute infection. In addition, NIAID is collaborating with the MHRP on two studies in Africa and Asia to screen and identify people very soon after HIV infection to expand knowledge of the pathophysiology of early infection, the location and size of newly established reservoirs, and the effect of early suppressive treatment on HIV reservoir size and clinical outcomes. Through the NIH Office of AIDS Research, NIAID is collaborating with investigators in China on the U.S.-China Program for Research Toward a Cure for HIV/AIDS program. This program supports collaborative research opportunities between investigators in the United States and China focused on basic research toward a cure for HIV/AIDS.

NIAID also continues to work closely with the Washington, D.C., Department of Health and the NIH Clinical Center to continue the D.C. Partnership for AIDS Progress, a collaborative research initiative designed to decrease the rate of new HIV infections in the city, improve the health of District residents living with HIV infection, and strengthen the city's response to the HIV/AIDS epidemic. The program, which could serve as a model for other U.S. cities with significant HIV burden, has reduced new infections by more than 50 percent in the last 8 years.

Co-morbidities

HIV infection is associated with significant end-organ morbidity, such as endothelial damage, neurocognitive defects, and renal failure. To understand the pathogenic mechanisms and test interventions, NIAID partners with the relevant NIH Institutes and Centers (ICs) that have subject matter experts in the relevant diseases in order to direct and support research in these areas. For example, and as previously mentioned, NIAID is collaborating with NHLBI on the REPRIVE study to explore whether cholesterol-lowering statin drugs will also improve the health of HIV-infected individuals. Furthermore, strong psychological, sociological, and structural factors combine to create vulnerabilities that promote HIV transmission and worsen the HIV pandemic. 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.

Implementation Science

Once effective interventions have been developed and licensed, other government agencies, such as the CDC, Health Resources and Services Administration, Office of the Global AIDS Coordinator, and USAID, are critical partners in designing research on the best approaches for implementing and scaling up those interventions. For example, NIAID, in collaboration with the Office of the Global AIDS Coordinator, NICHD, NIDA, NIMH, the National Institute on Nursing Research, and the National Institute on Alcohol Abuse and Alcoholism, funds an initiative to support implementation science research that will inform delivery and scale-up of efficacious interventions to improve HIV prevention, care, and treatment in Africa.

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.

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 affected by HIV/AIDS participate in all stages of planning and implementing HIV/AIDS research.

Area of Emphasis: Global health research on HIV/AIDS

NIAID supports HIV/AIDS research in resource-limited areas of the world with the greatest burden of disease, with the goal of developing safe and cost-effective prevention and treatment strategies. Many of these studies have dramatically changed how we prevent and treat HIV/AIDS around the world.

One important example of the global impact of NIAID-supported HIV research is the PROMISE study, which found that for HIV-infected women in good immune health, taking a three-drug regimen ("Option A") during pregnancy prevents MTCT more effectively than taking one drug during pregnancy, another during labor, and two more after giving birth. In 2016, the study also showed that both three-drug

maternal ART given to HIV-infected pregnant mothers and daily infant nevirapine were safe and highly effective at preventing HIV transmission during breastfeeding. In fact, infant deaths were extremely low in the study, with nearly all babies surviving their first year of life. These findings support the World Health Organization (WHO) guidelines that recommend lifelong ART for all pregnant and breastfeeding women living with HIV.

Another example is the NIAID-funded ASPIRE study. This Phase 3 microbicide clinical trial found that a vaginal ring containing the ARV dapivirine is safe and 27 percent effective for protecting against HIV infection. Further analysis has shown that for those who used the ring most consistently, the reduction in HIV infection was estimated to be as much as 75 percent or higher. The disparities in these results could be related to adherence to the ring protocol and/or age-related differences in susceptibility to HIV infection based on biological factors.

Examples of ongoing international clinical studies include:

- **HVTN 100:** In 2015, NIAID launched HVTN 100, a Phase 1/2 clinical trial in South Africa, to evaluate an investigational HIV vaccine regimen (a canary pox-based vaccine called ALVAC-HIV and a bivalent gp120 protein subunit vaccine). This vaccine regimen was designed to improve on the efficacy of the RV144 regimen. HVTN 100 is the first study conducted in collaboration with the P5. In May 2016, preliminary results from this study found that the improved vaccine regimen was safe and produced a robust immune response.
- **HVTN 702**: As a result of the preliminary results of HVTN 100, NIAID launched in 2016 a follow-up randomized controlled efficacy study known as HVTN 702. HVTN 702 is a large Phase 2b/3 efficacy study in South Africa to further evaluate the vaccine efficacy of the investigational regimen.
- The **HOPE/MTN-025 study**, a Phase 3b open-label extension of ASPIRE, aims to gain additional information on the safety and efficacy of a vaginal ring containing dapivirine. The study will also address how women use the ring, knowing that it can help reduce their risk of HIV infection; the relationship between adherence and HIV protection; and why the ring may work well as an HIV prevention strategy for some women but not others.
- The **START** trial is a large, randomized clinical trial designed to provide definitive evidence of the risks and benefits of early ART and to define more clearly the optimal time to begin treatment. The study is being conducted in 30 countries and has enrolled approximately 4,000 HIV-infected men and women who are 18 years old and older, have CD4 counts above 500 cells/mm^3, and have never taken ARVs. In 2015, the study demonstrated that immediate treatment with ART not only prevents serious AIDS-related diseases but also prevents the onset of cancer, cardiovascular disease, and other non-AIDS-related diseases and deaths. These results, and results from other studies, support offering ART to everyone who is infected with HIV.
- **HPTN 083**: In December 2016, NIAID launched HPTN 083, a Phase 2b/3 study to evaluate long-acting injectable cabotegravir for the prevention of HIV infection. This study will evaluate injections of cabotegravir given every 2 months compared with daily oral truvada as PrEP in approximately 4,500 men who have sex with men, and transgender women who have sex with men, in North and South America, Asia, and Africa. A second Phase 3 study (**HPTN 084**), which will evaluate long-acting cabotegravir for the prevention of HIV infection in young women, is anticipated to start in 2017.

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 people around the world.

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 BMGF, 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 HIV counseling and testing and prevention methods for those at risk of infection. By the end of December 2016, PEPFAR had provided ART to more than 11.5 million people infected with HIV, prevented approximately 2 million cases of MTCT through the distribution of ART, supported HIV testing and counseling for more than 74.3 million people, provided over 11.7 million voluntary male circumcisions in east and south Africa, and provided care and support for more than 6 million AIDS orphans.[4] As a result of these efforts, AIDS-related deaths have fallen by 45 percent since 2005 and the number of new infections among children has dropped by 50 percent since 2010. Because there are still approximately 2 million people who become infected with HIV each year, the need for expanded treatment access continues. NIAID has supported a number of PEPFAR-related activities such as providing staff expertise, management, and oversight of supplements to existing NIH grantees and supporting implementation science projects that aim to evaluate community-level testing, prevention, and treatment strategies.

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, please see the section on Global Health Research.

[4] The United States President's Emergency Plan for AIDS Relief [Internet]. U.S. Government. FY 2016 Global Results; 2017 [Accessed 2017 April 17]. Available from: www.pepfar.gov/documents/organization/264882.pdf.

Allergy, Immunology, and Immune-Mediated Diseases

The human immune system has evolved to protect against harmful pathogens in the 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. Components of the innate immune system survey their environment for infected or abnormal cells and have the capacity to mount a rapid and robust response to quickly contain a threat. 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 the body 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 harmless substances, including house dust mites, pollen, or foods such as peanut, can activate the immune system, leading to asthma, food allergy and other 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

Approximately 12.9 percent, or 39.5 million people, including 9.5 million children in the United States, have been diagnosed with asthma in their lifetimes.[5,6] African Americans have the highest prevalence rates, and children and adolescents younger than 18 years have higher rates than adults.[7] Among

[5] Bloom B, Simpson JL. Tables of Summary Health Statistics for U.S. Children: 2015 National Health Interview Survey. National Center for Health Statistics. 2016.
[6] Blackwell DL, Villarroel MA. Tables of Summary Health Statistics for U.S. Adults: 2015 National Health Interview Survey. National Center for Health Statistics. 2016.
[7] Ibid.

individuals whose family income is below the federal poverty level, the prevalence of asthma is almost 50 percent higher than that for individuals whose family income is at least twice the poverty level.[8]

Allergic Diseases

Allergic diseases include a wide range of chronic illnesses, such as food allergies, allergic rhinitis, and atopic dermatitis. The prevalence of seasonal and perennial allergic rhinitis in children 17 years old and younger is 17 percent, and this peaks at 20.8 percent in children 10–17 years old.[9] According to the CDC,[10] the prevalence of food allergies in children under age 18 increased from 3.4 percent between 1997 and 1999 to 5.1 percent between 2009 and 2011. Peanut is among the most common allergy-causing foods,[11] affecting an estimated 1 million children 17 years old and under, and is the leading cause of anaphylaxis and death due to food allergy. Children with food allergy are two- to four-fold more likely to have other allergic diseases, such as asthma, atopic dermatitis, and allergic rhinitis, than children without food allergy.

Autoimmune Disease

More than 80 autoimmune diseases have been identified, and collectively they are estimated to affect 5–7 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. Examples include:

- During 2008–2009 an estimated 18,000 people under the age of 20 in the United States were newly diagnosed with type 1 diabetes[12]
- An estimated 1.5 million Americans have RA[13,14]
- As many as 322,000 Americans have been diagnosed with, or are suspected of having, SLE,[15] which disproportionately afflicts African American women

Many other autoimmune diseases are rare and largely unknown, but collectively they affect a large number of individuals. In all cases, although treatments may alleviate symptoms, there are no cures, and

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[8] Jackson KD et al. Trends in allergic conditions among children: United States, 1997–2011. NCHS data brief, No. 121. Hyattsville (MD): National Center for Health Statistics. 2013.
[9] Ibid.
[10] Ibid.
[11] Boyce JA *et al.* Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol.* 2010 Dec;126(6 Suppl):S1-58.
[12] Centers for Disease Control and Prevention [Internet]. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services. Available from: www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
[13] Myasoedova E *et al.* Is the incidence of rheumatoid arthritis rising?: Results from Olmsted County, Minnesota, 1955–2007. *Arthritis Rheum.* 2010 Jun;62(6):1576-82.
[14] Helmick CG *et al.* Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. *Arthritis Rheum.* 2008 58(1):15-25.
[15] Laurence RC *et al.* Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998 41:778.

the incidence of many autoimmune diseases appears to be increasing for reasons that are not yet understood.

Transplantation

Approximately 33,000 organ transplants are performed each year in the United States, but more than 118,000 people are on waiting lists for organs. Despite tremendous progress, several barriers remain to the overall success of transplantation. Survival rates after transplantation surgery have improved markedly, but there has been little improvement in arresting or reversing the long-term decline in the function of transplanted organs. End-stage failure of transplanted organs occurs as a result of drug toxicity, chronic allograft rejection, and progression of underlying disease.

The success of current antiretroviral treatments for HIV created a new population of HIV-positive patients who require organ transplantation. Whether due to chronic complications of treatment, co-infection, or the fact that they are living considerably longer, these patients require solid organ transplant and are creating additional demands on an already scare resource. Until recently, harvesting organs from HIV-positive donors was strictly prohibited; HIV-positive patients had to receive organs from HIV-negative donors. The passage of the HIV Organ Policy Equity Act in 2013 changed this and allowed HIV-positive donor organs to be transplanted into HIV-positive recipients participating in clinical research.

Research in Basic Immunology

The NIAID 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 due to 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, 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 advances.

To meet this challenge, the NIAID research portfolio has evolved to include increased emphasis on human immunology. The complex synthesis of mouse and human studies is enabled by the emergence of new technologies, advances in systems biology approaches, expanded capabilities in bioinformatics, and the development of sophisticated data analysis and computational modeling 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.

Area of Emphasis: Apply knowledge of basic immunology to support the NIAID mission 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 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. An additional emphasis is on more fully understanding the immune system in infants to protect them from infection and to develop more effective vaccines. NIAID is continuing to expand programs to discover and develop adjuvants, components of vaccines that enhance the immune response, that are safe and effective when formulated as components of vaccines intended for different age groups or immunocompromised patients. NIAID also has increased its focus on the role of the environmental and organ-specific microbiome in the prevention and treatment of allergic and autoimmune diseases. As part of its commitment to improving disease outcomes, NIAID also supports programs to identify biomarkers of disease progression or transplant rejection and characterize gene variants and expression patterns that predict therapeutic outcomes in immune-mediated disorders and organ transplantation.

PRIORITY 1: Continue supporting research in basic immunology.

- Identify novel pathways of immune protection and disease susceptibility in animal models and explore their potential as targets for therapeutic intervention and drug and vaccine development
- Promote the development and use of novel mouse models that more closely represent human immune responses for in-depth mechanistic studies
- Apply and develop advanced technologies, including computational modeling, to expand knowledge in basic immunology and of the human immune response

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, allergic, and autoimmune diseases.

- Understand the underlying mechanisms involved in the immune response to infection or vaccination in neonates and infants and the consequences of exposure to infectious agents *in utero* or in infancy on immune system development and function later in life
- Advance the role of the environmental and organ-specific microbiome in the prevention and treatment of allergic and autoimmune diseases and transplant rejection

PRIORITY 3: Identify vaccine adjuvants that enhance vaccine activity or modulate detrimental immune responses.

- Advance promising adjuvant candidates through optimization and preclinical testing
- Evaluate novel combinations of distinct, well-characterized adjuvants for their synergistic activity in vaccine responses
- Assess immunoregulatory and immunoinhibitory properties of adjuvant candidates for use in treatment or prevention of immune-mediated diseases

- Discover and develop vaccine adjuvants or adjuvant combinations that lead to more durable protection to address waning of vaccine-induced immunity

PRIORITY 4: Apply knowledge of lymphocyte trafficking, tissue homing, and mucosal immunology to facilitate the design of vaccines and immunotherapies that protect mucosal surfaces from infection and immune-mediated diseases.

PRIORITY 5: Develop novel strategies for earlier detection, diagnosis, treatment, and prevention of immune-mediated diseases.

PRIORITY 6: Develop and enhance approaches through preclinical research to extend the survival of transplants.

Area of Emphasis: Support clinical trial networks dedicated to treating and preventing allergic and autoimmune diseases and to preventing graft rejection

The NIAID clinical trial networks remain at 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. The Learning Early About Peanut Allergy (LEAP) study demonstrated that introduction of peanut products into the diets of infants at high risk of developing peanut allergy was safe and led to an 81 percent relevant reduction in subsequent development of the allergy. NIAID is committed to expanding on this result to explore the mechanism of peanut allergy prevention, maintenance of peanut tolerance, and strategies to prevent other food allergies. Another focus is on cellular therapies in transplantation and the treatment of autoimmune diseases. Recently, the High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplant for Relapsing-Remitting Multiple Sclerosis (HALT-MS) Study demonstrated that high-dose immunosuppressive therapy followed by transplantation of a person's own blood-forming cells induced long-term remission of active relapsing-remitting multiple sclerosis at 5 years. Network-sponsored clinical trials include mechanistic studies to better understand the immunological basis for clinical outcomes.

PRIORITY 1: Design and conduct clinical trials that demonstrate the safety and efficacy of novel tolerance-inducing therapies for allergic diseases and asthma.

- Develop immune intervention strategies for the treatment and prevention of food allergy, especially childhood milk, egg, and peanut allergy
- Design and conduct clinical trials on allergen immunotherapy for allergic diseases, including asthma
- Identify the genes associated with food allergy and atopic dermatitis
- Identify factors that influence prevalence rates and severity of pediatric asthma and allergic diseases among socioeconomically disadvantaged children and diverse ethnic populations

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

- Characterize the interactions of the microbiome and its relationship to host immune function
- Develop innovative approaches to enhance mucosal and systemic responses
- Characterize host factors that affect suitable transplant donor and recipient matches

PRIORITY 3: Support clinical evaluations of immune-based treatment, including cellular therapies, tolerance approaches, and other strategies to treat autoimmune diseases and improve transplant outcomes.

- Further evaluate the use of human pancreatic islets for the treatment of severe hypoglycemia in the setting of type 1 diabetes
- Further evaluate the use of cellular therapies in the treatment of autoimmune diseases, including severe combined immunodeficiency, scleroderma, and multiple sclerosis

PRIORITY 4: Explore modification of the human microbiome and indoor environment to alter early childhood exposure to aeroallergens and microbial products that could alter development and progression of childhood allergy.

PRIORITY 5: Support clinical evaluations with associated mechanistic studies of organ transplantation for treatment of organ failure secondary to chronic HIV infection.

- Characterize the interaction of ARVs and immunosuppressive agents in HIV-infected transplant recipients, allowing for rational treatment regimens
- Conduct HIV-positive donor to HIV-positive recipient organ transplants to evaluate the feasibility, effectiveness, and safety of such transplants

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

The recent and expanding investment by NIAID in bioinformatics has greatly enhanced understanding of human immune regulation. For example, NIAID launched a program to better understand the impact of the human microbiome on the regulation of the immune response at mucosal surfaces. Additionally, NIAID established and continues to expand the Human Immunology Project Consortium and the Cooperative Centers in Human Immunology, in which participating investigators are collectively defining the mechanisms responsible for regulating the immune response in health and in response to infection or vaccination. 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.

- Conduct comprehensive profiling of immune responses to infections or vaccines across multiple age groups, from the very young to the elderly, and for a variety of infectious pathogens, to advance the development of new or improved vaccines and therapeutics
- Advance understanding of the effects of aging on immune function and response to infection or vaccines
- Conduct mechanistic studies to better understand the strength and breadth of, and the requirements for, maintaining immune responses to vaccines or after infections
- Expand the identification and understanding of the molecular causes of primary immunodeficiency diseases

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.

PRIORITY 4: Accelerate the development and validation of sample-sparing assays in the study of the human immune system in health and disease.

Global Health Research

Unlike other NIH Institutes, NIAID is mandated not only to maintain and grow a robust basic and applied research portfolio in microbiology, infectious diseases, immunology, and immune-mediated diseases but also to respond rapidly to emerging and re-emerging disease threats wherever they occur in the world. To comprehensively execute this mandate, which helps to protect the American people from emerging health threats, NIAID must support and conduct the best research possible, wherever scientific opportunities present themselves. The Institute also must be well-prepared to rapidly mount an effective research response whenever emerging and re-emerging infectious diseases threaten U.S. and global public health. On behalf of the U.S. government, NIAID provides global leadership to assure that U.S. priorities are addressed through international collaborative research, to influence global research strategies and priorities, to help enhance infectious disease and immunology research capacity, and to establish productive relationships with other leading biomedical scientific organizations around the world.

In today's world with its dramatic expansion of international travel and increasing human exposure to new and emerging diseases that can rapidly reach the United States, maintaining an ability to anticipate and effectively respond to health threats is essential to Americans' well-being and productivity. Infectious diseases that emerge or are endemic in distant regions can quickly threaten the health, social, and economic stability of the United States and other nations, as has occurred with emerging epidemics or recent outbreaks of avian influenza, HIV/AIDS, drug-resistant TB and malaria, measles, MERS, Ebola, dengue, chikungunya, and Zika. To effectively prepare for and respond to these inevitable international infectious disease challenges, research must be pursued through mutually beneficial partnerships that engage U.S. scientists and scientists and institutions in countries where threatening infectious diseases occur or are likely to emerge. Assuring effectiveness in global infectious disease research preparation and response requires shared scientific leadership, a commitment to long-term sustainability, and the engagement of local communities.

Since its establishment, NIAID-supported global health research has yielded critically important basic science advances as well as new or improved diagnostics, drugs, and vaccines. Therefore, NIAID continues to be committed to well-designed, ethical, global studies that support the development of evidence-based and effective medical countermeasures against infectious diseases. These studies must keep pace with technological innovations and expanding opportunities in infectious disease and immunology research, including opportunities created by unpredictable disease outbreaks. To facilitate global research in a challenging economic environment, NIAID also leads the way in developing cost-sharing research funding strategies that enhance the resources available to American scientists and their foreign collaborators engaged in infectious disease and immunology research. Such arrangements also contribute to bilateral and multilateral engagement and scientific diplomacy.

Area of Emphasis: Develop, foster, and maintain international scientific collaborations

In recent years, the most productive biomedical research involves international collaborations. For American infectious disease scientists, international cooperation is often essential, especially for clinical studies and trials. Therefore, fostering and supporting international scientific collaborations is critical to the successful execution of the NIAID mission. Facing significant scientific and logistic challenges, NIAID has a history of maintaining productive international collaborations while also pursuing opportunities to expand this effort. Innovative approaches to identify and foster international research cooperation have been pioneered by NIAID through targeted outreach workshops, small collaborative grant solicitations, and shared funding strategies that have engaged partner countries and organizations to help ensure stable, long-term collaborations.

For example, to generate new scientific collaborations focused on threats to the southern United States, NIAID has convened targeted scientific conferences on dengue, chikungunya, and Zika viruses. As a result, the first special journal issue on chikungunya research has been produced, four collaborative dengue research grants have been awarded, and major Zika virus studies have been launched with Brazilian co-funding. The findings from these studies will help guide Zika disease management in the United States and globally.

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: Assure U.S. leadership and effective science diplomacy in the fields of infectious disease and immunology research to help guide a global focus on high-priority research and evidence-based public health and clinical practice.

PRIORITY 3: Support and establish targeted co-funded 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 4: Identify and develop collaborative research in regions where unusual opportunities emerge and where scientific collaboration previously has been limited, including 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.

PRIORITY 6: Respond to emerging or re-emerging infectious disease outbreaks by conducting essential research and enhancing research capacity to foster discovery both during and after the outbreak.

Area of Emphasis: Participate in the global response to significant outbreaks of new and emerging diseases through research and development

NIAID has a central role in conducting medical countermeasure research and development in the context of an international disease outbreak. This research is essential to help bring the outbreak under control and to develop diagnostics, therapeutics, and vaccines to prevent or curtail future outbreaks. In this effort, NIAID uses a well-designed approach, based on sound scientific principles and practices. The rapid completion of high-quality studies that will enable licensure of products allows the greatest number of patients to be treated with safe and effective vaccines, drugs, and diagnostics as quickly as possible. To prepare for such research needs, NIAID emphasizes the enhancement or establishment of multifaceted clinical trials infrastructure so that collaborative relationships and required research tools are immediately available to be activated during times of urgent need. To assure that the United States and other countries can most effectively respond to emerging or new diseases over time, NIAID undertakes or supports research and development activities that produce results that can lead to the successful regulatory assessment of a product's safety, efficacy, and utility as a long-standing, fully approved medical intervention.

NIAID has continued to enhance and expand research capacity around the world to enable high-quality scientific collaboration and to prepare for the research response required in an infectious disease outbreak. In 2014, as the Ebola outbreak in West Africa became a global crisis, NIAID leadership and scientists launched clinical trials of promising Ebola vaccine candidates and treatment strategies. In 2016, as Zika virus infection and its complication of microcephaly in babies of infected mothers spread throughout the Caribbean and Central and South America, NIAID rapidly developed a study on Zika in infants and pregnancy and launched clinical trials of preventive Zika vaccines.

PRIORITY 1: Conduct research of the highest quality to accurately evaluate the safety and efficacy of countermeasures that can be used to treat and prevent illness or diagnose individuals in the face of emerging and re-emerging infectious disease outbreaks.

PRIORITY 2: Study candidate medical countermeasures in priority order with transparent and measurable consensus objectives to advance development of promising vaccines, drugs, and diagnostics.

PRIORITY 3: Enhance capabilities, such as clinical trials infrastructure, well in advance of the time of emergency, so that these capabilities are fully functional when needed.

PRIORITY 4: Help coordinate efforts among U.S. government agencies to ensure that resources such as biocontainment facilities, reagents, specimens, and data are available for response to an outbreak.

PRIORITY 5: Utilize risk communication and community engagement strategies to effectively mount a community-based approach to undertake research during an outbreak.

PRIORITY 6: Maintain active collaborations with other U.S. government agencies, international organizations, and philanthropic entities concerned with infectious disease research by participating in coordination activities and through international programs such as the Global Health Security Agenda.

PRIORITY 7: Promote and engage in scientific discussions to identify needs, priorities, and opportunities for research on emerging or re-emerging infectious diseases.

Area of Emphasis: Enhance research capacity where scientific opportunities exist

The individuals who conduct, support, and participate in international health research are critical for ensuring the success of studies and sustaining productive research sites. In addition, they serve as key monitors of local scientific opportunities, emerging new diseases, and potential outbreaks. In these latter situations, collaboration with local researchers allows NIAID to respond rapidly to emerging and re-emerging infectious diseases. 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 beliefs.

Capable, well-trained administrative staff, research support resources, policies, and procedures must be in place to ensure efficient, effective, and ethical management of sustainable, multidisciplinary 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 also 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 individual studies.

The NIAID HIV/AIDS Clinical Trials Networks are a prime example that reflects how the Institute's research and administrative staff and flexible infrastructure foster ability to advance disease prevention, treatment, and vaccine development. The Networks have significantly expanded research capacity worldwide through mentorship and scientific engagement. Using this infrastructure, NIAID is also supporting studies on TB and hepatitis C, common co-infections in HIV-positive individuals.

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 strengthen foreign scientists' and institutions' ability to implement high-quality research, comply with appropriate administrative and fiduciary requirements, and manage complex laboratory and field-site challenges, including the safe and secure 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: Expand networks of U.S. and foreign investigators to enhance research capacity by fostering international scientific leadership through mentoring and career partnerships.

Area of Emphasis: Engage international research partnerships and influence policies

Through its global health investment, NIAID has had an impact on research policy and practice, often working in partnership with others. Such collaborations, often involving HHS, other U.S. government agencies, and international governmental and nongovernmental organizations, help NIAID accomplish its mandate and enhance its global research activities.

In recent years, NIAID has enhanced collaborations with other NIH ICs that share a global research interest. Other key partnerships include the CDC, the Department of Defense, and large philanthropic organizations such as BMGF and the Wellcome Trust. NIAID collaborates with organizations that have a shared vision and can complement investments by NIAID to advance global health research.

The NIH and the South African Medical Research Council (SA-MRC) Joint Collaborative Program, established in 2013, is a jointly funded five-year research program in HIV, TB, and cancer research. This trans-NIH program involves four Institutes and one Center that each contribute funding. Matching SA-MRC funds have been donated to NIH so that the program can be managed by NIH following its standards and practices. Thirty collaborative grants are being implemented, engaging leading U.S. and South African scientists.

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.

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 the NIAID global health agenda.

PRIORITY 6: Ensure integration of 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 agenda 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 the NIAID 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 the challenges of international involvement and emerging opportunities. Global research requires significant funding, as well as 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. The NIAID commitment to international research is reflected in the actions of its director, the Institute's strategic priorities, and the programs implemented by the Institute as it pursues scientific opportunities throughout the world to improve the health of Americans and of individuals worldwide.

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 investigators 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 antibiotic-resistant bacteria, and probe the functions and dysfunctions of the human microbiome. The NIAID 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 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 vaccines 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, animal models of infectious diseases, and therapeutic and vaccine testing and evaluation services.

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 eligible 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 continues to refine its clinical trials networks to 1) foster 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, immunology, and systems biology, to advance discovery in HIV/AIDS and HIV-associated infections and co-morbidities
- 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 capacity and clinical research expertise required to translate scientific discoveries into clinical advances and to correlate biologic factors with clinical outcomes.

PRIORITY 5: Foster and support community engagement 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.

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: Support bioinformatics efforts 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

To develop and support the next generation of biomedical researchers, the Institute offers a variety of research training and career development programs. These programs enable promising scientists, from those in graduate school, postdoctoral, or postgraduate clinical positions, or among the ranks of junior faculty, to gain biomedical research experiences leading to prominent research careers. These programs also contribute to increasing the participation of scientists from groups underrepresented in biomedical research.

Sustaining a broad research program requires support to help new and early-stage 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.

Furthermore, NIAID staff seek to gain insight on current research training and career development trends by directly listening to our grantees and awardees. We host key workshops to engage the research training community and seek ways they think we can improve our research training and career development programs. These workshops also inform grantees about key policy and programmatic changes.

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 these investigators 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. Attract the next generation of biomedical researchers through outreach activities via workshops and training sessions at national scientific meetings, as well as local graduate and medical school student conferences.

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, healthcare 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.