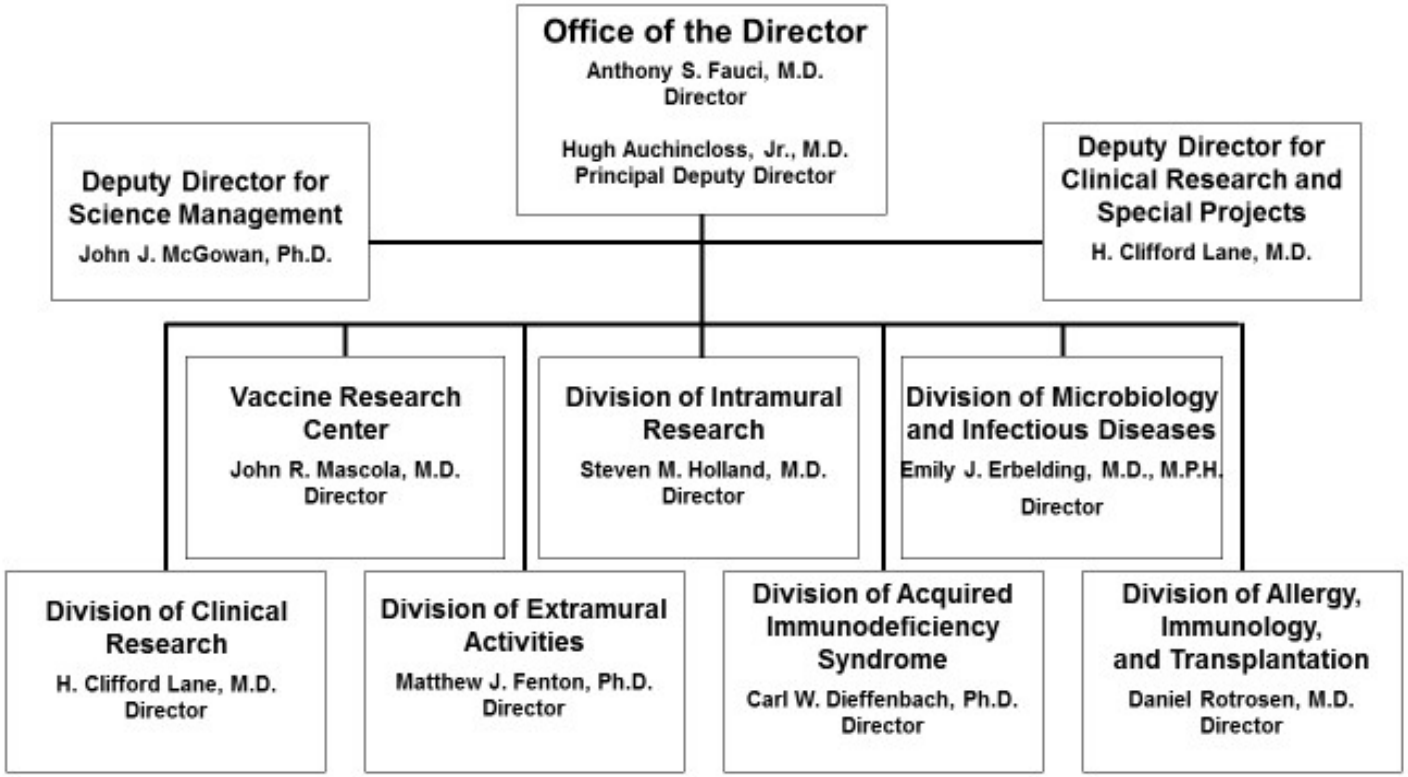
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases (NIAID)

NOTE: The FY 2018 Annualized CR funding amounts cited throughout this chapter reflect the effects of no OAR HIV/AIDS Transfers.

National Institute of Health
National Institute of Allergy and Infectious Diseases
Organizational Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

For carrying out section 301 and title IV of the PHS Act with respect to allergy and infectious diseases, $4,761,948,000.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

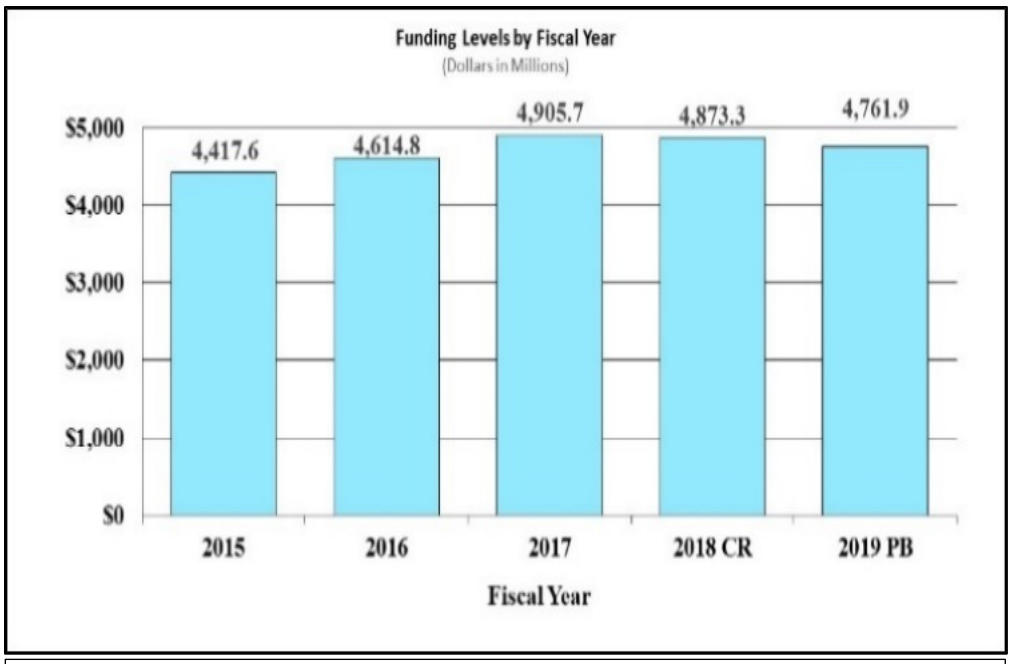
Amounts Available for Obligation[1]
(Dollars in Thousands)

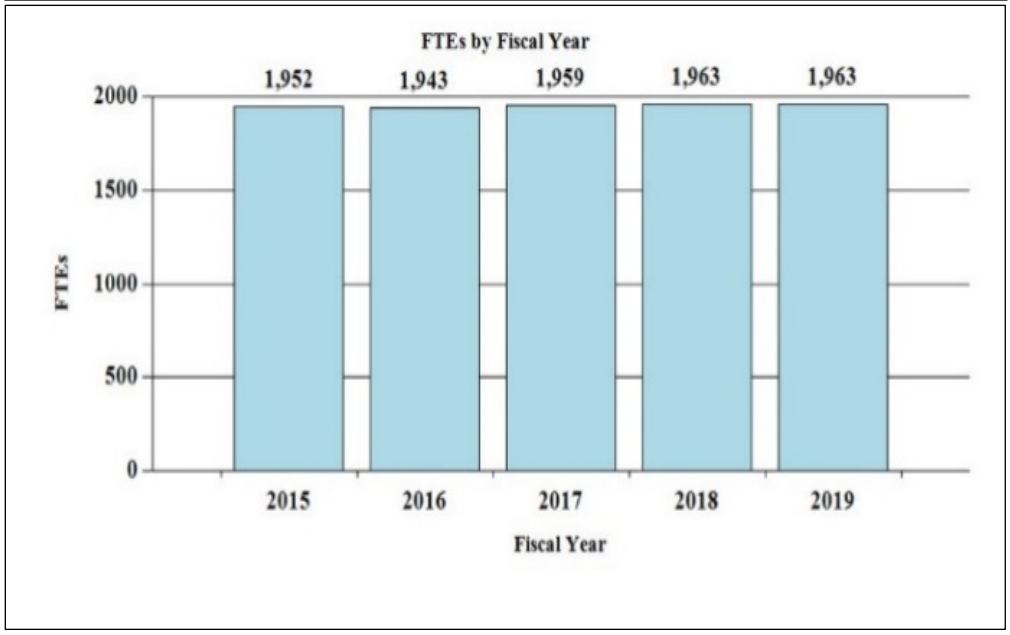
Source of Funding	FY 2017 Final	FY 2018 Annualized CR	FY 2019 President's Budget
Appropriation	$4,906,638	$4,906,638	$4,761,948
Mandatory Appropriation: (non-add)			
Type 1 Diabetes	*(0)*	*(0)*	*(0)*
Other Mandatory financing	*(0)*	*(0)*	*(0)*
Rescission	0	-33,321	0
Sequestration	0	0	0
Secretary's Transfer	-10,628		
Subtotal, adjusted appropriation	$4,896,010	$4,873,317	$4,761,948
OAR HIV/AIDS Transfers	9,708	0	0
Subtotal, adjusted budget authority	$4,905,718	$4,873,317	$4,761,948
Unobligated balance, start of year	0	0	0
Unobligated balance, end of year	0	0	0
Subtotal, adjusted budget authority	$4,905,718	$4,873,317	$4,761,948
Unobligated balance lapsing	-10	0	0
Total obligations	$4,905,708	$4,873,317	$4,761,948

[1] Excludes the following amounts (in thousand) for reimbursable activities carried out by this account:
FY 2017 - $20,913 FY 2018 - $20,913 FY 2019 - $17,776

Fiscal Year 2019 Budget Graphs

History of Budget Authority and FTEs:





NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2018 Amount Authorized	FY 2018 Annualized CR	2019 Amount Authorized	FY 2019 President's Budget
Research and Investigation	Section 301	42§241	Indefinite	$4,873,317,021	Indefinite	$4,761,948,000
National Institute of Allergy and Infectious Diseases	Section 401(a)	42§281	Indefinite		Indefinite	
Total, Budget Authority				$4,873,317,021		$4,761,948,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation
2009	$4,568,778,000	$4,716,283,000	$4,688,828,000	$4,702,572,000
Rescission				$0
2010	$4,760,295,000	$4,859,502,000	$4,777,457,000	$4,818,275,000
Rescission				$0
2011	$4,977,070,000		$4,969,301,000	$4,818,275,000
Rescission				$42,307,326
2012	$4,915,970,000	$4,915,970,000	$4,725,288,000	$4,499,215,000
Rescission				$8,503,516
2013	$4,495,307,000		$4,508,932,000	$4,490,711,484
Rescission				$8,981,423
Sequestration				($225,402,837)
2014	$4,578,813,000		$4,548,383,000	$4,358,841,000
Rescission				$0
2015	$4,423,357,000			$4,358,841,000
Rescission				$0
2016	$4,614,779,000	$4,512,918,000	$4,710,342,000	$4,629,928,000
Rescission				$0
2017[1]	$4,715,697,000	$4,738,883,000	$4,961,305,000	$4,906,638,000
Rescission				$0
2018	$3,782,670,000	$5,005,813,000	$5,127,866,000	$4,906,638,000
Rescission				$33,320,979
2019	$4,761,948,000			

[1] Budget Estimate to Congress includes mandatory financing.

Justification of Budget Request

National Institute of Allergy and Infectious Diseases

Authorizing Legislation: Section 301 and title IV of the Public Health Service Act, as amended.

Budget Authority (BA):

	FY 2017 Final	FY 2018 Annualized CR	FY 2019 President's Budget	FY 2019 + / - FY 2018
BA	$4,905,718,000	$4,873,317,021	$4,761,948,000	-$111,369,021
FTE	1,959	1,963	1,963	0

Program funds are allocated as follows: Competitive Grants/Cooperative Agreements; Contracts; Direct Federal/Intramural and Other.

Director's Overview

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. NIAID's broad research portfolio advances our knowledge of pathogen biology and the host response to microbes, and of the healthy immune system and its dysfunction that underlies allergy, asthma, autoimmune diseases, and transplant rejection. The diagnostics, vaccines, and therapeutics discovered, designed, developed, or improved with NIAID support form a potent arsenal of medical countermeasures that can be used to protect and treat individuals worldwide.

NIAID is committed to its unique dual mandate: to advance basic and applied research on endemic infectious diseases and to respond to emerging and re-emerging public health threats. The rapid spread of Zika virus infections across the Americas in 2015–2016 highlighted how quickly public health can be threatened as new pathogens emerge or familiar ones re-emerge with new properties. In response to this threat, NIAID swiftly mobilized its flexible infrastructure and collaborative research partnerships to help develop several promising Zika vaccine candidates. Two of these vaccine candidates, including one developed by researchers at the NIAID Vaccine Research Center (VRC), are currently in clinical trials in the United States and internationally. NIH-supported studies to investigate Zika infection in pregnant women and infants are currently enrolling participants and should answer important questions regarding the risk of infection to the developing fetus, and the longer-term impact on affected children. Recent experience in providing a research response to several international public health emergencies underscores the need to anticipate potential threats and support tailored tools to address them, and to develop broad-based research solutions for the unidentified emerging pathogens to come. Through continual efforts to prepare for potential disease threats, NIAID stands ready to lead the biomedical research response to emerging threats and protect public health.

A sustained research effort since the early 1980s, when HIV was first identified, has brought the goal of an "AIDS-free generation," one in which new HIV infections and deaths from HIV are rare, within reach. Lifesaving antiretroviral therapy (ART) has led to marked reductions in deaths and illness due to HIV and its associated coinfections, comorbidities, and other complications. Large studies have shown that when HIV is suppressed by ART to undetectable levels in an infected person, the virus does not transmit to that person's uninfected sexual partner. Because adherence to daily treatment is challenging for many people living with HIV/AIDS, NIAID is developing long-acting antiretroviral drugs through its Long-Acting/Extended Release Antiretroviral Resource Program (LEAP). It is hoped that the resulting products will be easier to use, less toxic, and more cost effective than current treatments. A large-scale NIAID-supported clinical trial seeks to determine whether a long-acting injectable drug, cabotegravir, given every eight weeks, is as effective as daily, oral Truvada®—the only drug currently licensed for use as pre-exposure prophylaxis (PrEP)—in protecting men and transgender women from HIV infection. A companion study will test the safety and efficacy of injectable cabotegravir for HIV prevention in young women.

Influenza continues to place a substantial health and economic burden on the United States and countries worldwide. NIAID supports a comprehensive research portfolio to better understand the immune responses to influenza infection and vaccination, and to develop more effective vaccines and immune response–boosting adjuvants. These efforts include multiple strategies to develop vaccines that can generate durable protection against seasonal and pandemic influenza strains, with the ultimate goal of creating a "universal" influenza vaccine, a top priority for NIAID. To help advance this goal, NIAID convened a June 2017 workshop at which experts from various disciplines identified key research gaps and potential solutions. The workshop findings will inform a NIAID universal influenza vaccine strategic plan and research agenda.[1] NIAID's work toward a broadly effective influenza vaccine reflects the NIH Director's theme "Investing in Translational and Clinical Research to Improve Health."

Countering the growing global problem of antimicrobial resistance (AMR) is another top NIAID research priority. Since NIAID established the Antibacterial Resistance Leadership Group (ARLG) in 2013, the group has systematically developed, prioritized, and implemented a clinical research agenda to address the growing public health threat of antibiotic resistance. The ARLG launched the prospective, multicenter clinical study, Consortium on Resistance against Carbapenems in *Klebsiella pneumoniae* and Other Enterobacteriaceae (CRACKLE), to better understand the risks and infection outcomes pertaining to carbapenem-resistant Enterobacteriaceae and to identify barriers to patient enrollment in clinical trials. NIAID-supported researchers also identified novel antibiotics, known as humimycins, with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria and identified a bacterial ecosystem that could be used as protective probiotics against *Clostridium difficile* infection. Furthermore, NIAID-funded clinical trials suggest that two inexpensive FDA-approved antibiotics are effective in treating MRSA skin infections, including abscesses, countering the belief that antibiotics provide little help for MRSA skin infections. NIAID also is a partner in

[1] Paules C.I., Marston H.D., Eisinger R.W., Baltimore D., and Fauci A.S. The research pathway to a universal flu vaccine. *Immunity*. 2017 Oct 17; 47(4):599-603.

the Combating Antibiotic-Resistant Bacteria Accelerator (CARB-X) program, a global public-private partnership focused on speeding the development of treatments for the world's most serious bacterial threats.

NIAID continues to support research on the pathogenesis, treatment, and prevention of immune-mediated diseases as well. For example, one recently reported clinical trial focused on treatment of multiple sclerosis (MS), a progressive disease of the central nervous system. This trial, which enrolled patients who did not respond to standard medical care, combined immunosuppressive therapy with transplantation of a person's own stem cells. In the five years after stem cell transplantation, more than 86 percent of the participants experienced no further loss of neurological function, relapse, or new neurological lesions. Another NIAID-supported stem cell therapy has shown promise in treating diffuse cutaneous systemic sclerosis, a fatal autoimmune disease in which the function of the skin, blood vessels, or internal organs is compromised by hardening of the tissues. In this study, the Scleroderma: Cyclophosphamide or Transplant (SCOT) trial, patients who received transplants had increased survival rates and improved long-term outcomes compared with patients treated with cyclophosphamide. NIAID also is advancing research on solid organ transplantation for HIV-infected patients. The HIV Organ Policy Equity Act in 2013 enabled organs to be transplanted from HIV-positive (HIV+) donors into HIV+ recipients. NIAID worked with a national network of transplant surgeons to develop clinical protocols for HIV+ kidney transplantation trials that will begin enrollment in FY 2018. NIAID also is developing clinical trial protocols for liver transplantation involving HIV+ individuals.

In FY 2019, NIAID will support opportunities for new researchers to receive funding equivalent to those of established investigators submitting new R01 applications. NIAID will continue to support basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses, including illness from emerging infectious diseases, agents with bioterrorism potential, HIV/AIDS, influenza, tuberculosis, malaria, autoimmune disorders, drug-resistant microbes, asthma, and allergies.

The NIAID's Intramural Research and Research Management and Support programs reflect a modest increase for pay and benefits and reductions in the non-pay categories consistent with the overall reduction in budgetary resources and NIH budget policy.

Program Descriptions and Accomplishments

HIV/AIDS

In the 36 years since AIDS was recognized, the disease has claimed more than 35 million lives, and it remains one of the most devastating pandemics in human history.[2] With approximately 1.8 million people newly infected each year worldwide,[3] including an estimated 37,600 in the United States,[4] improving HIV prevention through innovations in testing, monitoring, targeting, and modeling remains an essential focus. NIAID-sponsored research has helped pave the way for strategies to prevent perinatal HIV transmission: transmission from mother to child during pregnancy, childbirth, and breastfeeding. In the absence of any intervention, rates of mother-to-child HIV transmission historically have ranged from 15 to 45 percent, according to the World Health Organization (WHO). Recent results from the NIAID-funded Promoting Maternal and Infant Survival Everywhere (PROMISE) study demonstrated that providing either one of two highly active three-drug ART regimens to mothers and the anti-HIV drug nevirapine to infants during breastfeeding resulted in HIV transmission rates between 0.3 and 0.6 percent from six months to one year of age. These results provide a roadmap to end perinatal HIV transmission and strongly support the WHO recommendation to provide a three-drug anti-HIV regimen to all pregnant HIV-infected women. NIAID continues to support and conduct research to prevent perinatal HIV transmission while assuring the health of both mother and child.

Identifying safe and effective prevention strategies is critical in the fight against HIV/AIDS and in ending the HIV/AIDS pandemic. Existing proven prevention methods include condoms, voluntary adult medical male circumcision, PrEP, syringe exchange, and treatment of HIV-infected persons with ART. NIAID is supporting research to develop new agents, sustained release formulations, drug combinations, and delivery methods such as vaginal rings or injectable forms of ART; determining the impact of different dosing regimens; and assessing the impact of PrEP in specific populations and in the broader population. A large NIAID-funded trial known as A Study to Prevent Infection with a Ring for Extended Use (ASPIRE) showed that a vaginal ring containing the antiretroviral drug dapivirine safely reduced the risk of HIV infection by 37 percent overall and by 61 percent in women ages 25 and older in sub-Saharan Africa. The ring did not protect the youngest women, likely due to low adherence to this method. Several studies are evaluating prospects for improving adherence. NIAID continues to address the needs of women by advancing the development of next-generation prevention tools, with an emphasis on contraceptive-compatible, long-acting strategies.

A small subset of people living with HIV naturally produce broadly neutralizing antibodies (bNAbs) that target multiple, diverse HIV strains. These bNAbs do not clear the virus in these individuals; however, they have been shown in the laboratory to stop most HIV strains from infecting human cells, and to protect animal models from infection. As NIAID scientists identify increasingly potent bNAbs, studies are underway to test them in humans. The Antibody-

[2] WHO fact sheet No. 360, updated July 2017. http://www.who.int/mediacentre/factsheets/fs360/en/
[3] Ending AIDS: Progress towards the 90-90-90 targets. UNAIDS, 20 July 2017. http://www.unaids.org/en/resources/documents/2017/20170720_Global_AIDS_update_2017
[4] HIV in the United States: At a Glance, updated Oct. 11, 2017. Centers for Disease Control. https://www.cdc.gov/hiv/statistics/overview/ataglance.html

Mediated Prevention studies are evaluating whether infusing a bNAb every eight weeks is safe and effective at preventing HIV infection. NIAID also has partnered with GlaxoSmithKline to determine which bNAbs are most promising for future development. These products may also be effective as treatment: Injection of two bNAbs shortly after infection enabled some infected monkeys to control an HIV-like virus for more than six months. In addition, investigators at NIAID and Sanofi created a bNAb that targets three critical sites on HIV and protects monkeys from infection by two different SHIV strains, a monkey form of HIV. NIAID will test this antibody in humans, both as a prevention strategy and as a treatment. Planned programs analyzing the evolution of HIV in high-transmission population clusters, and the role of the microbiome in HIV susceptibility, will further inform the development of new prevention approaches.

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. A clinical trial is underway to examine whether a modified version of the RV144 vaccine regimen, which was the first to show modest protection against HIV infection, can provide greater and more sustained protection. NIAID also is testing "mosaic" vaccine candidates designed to protect against many HIV subtypes. Other NIAID-supported studies aim to develop potential vaccines that induce bNAbs, which may prevent infection. Two large, early-stage clinical trials examined combinations of immunogens (molecules designed to induce an immune response, in this case bNAbs). The combination most effective in animal models was also the most effective in humans. NIAID-supported scientists recently elicited bNAbs in cattle rapidly through immunization. Understanding how these potent bNAbs are created will inform HIV vaccine design. NIAID is launching a large, multidisciplinary consortium to further support preclinical vaccine discovery and development.

Thanks to advances in therapeutics, HIV-positive individuals are living longer and thus experiencing diseases associated with aging. To address this, NIAID is supporting research on HIV-associated co-morbidities, as well as on common HIV-associated co-infections, such as tuberculosis (TB). NIAID and NHLBI are supporting a multicenter international clinical trial to test whether statin drugs can reduce the risk of major heart attacks, strokes, and cardiovascular disease in people living with HIV. In a basic research advance, NIAID scientists identified a mechanism of abnormal blood clotting in HIV-infected cells and animals and blocked this with an experimental drug.

NIAID will continue to support research from basic discovery through clinical trials on vaccine candidates as well as other prevention strategies. Continuations of key research activities include advancing vaccine discovery, identifying novel approaches to interrupt HIV transmission, increasing understanding of the complex interactions of HIV with the immune system by using a systems biology approach, focusing on the discovery of the mechanisms of latency and persistence of HIV in the human body, and supporting manufacturing capacity and processes for biological based prevention strategies.

Program Portrait: Achieving Sustained Antiretroviral Therapy–Free Remission of HIV

The profound and durable suppression of HIV by ART represents a major accomplishment in HIV/AIDS research. However, low levels of HIV persist in patients on long-term ART, and the virus almost always rebounds if treatment is stopped. Furthermore, lifelong ART is associated with toxicity, residual chronic inflammation, and the accelerated onset of diseases associated with aging. NIAID is therefore pursuing alternatives to lifelong ART, with the goal of achieving sustained ART-free HIV remission.

One approach is to administer or induce the production of so-called broadly neutralizing antibodies (bNAbs) that block a high percentage of global HIV strains from infecting human cells and facilitate the killing of cells already infected. A recent early-phase clinical trial led by NIAID found that the bNAb VRC01 can safely be administered to people living with HIV. In addition to this treatment approach, two large multinational clinical studies are now underway to evaluate intravenous delivery of VRC01 for preventing HIV infection.

Another approach is to target the small amount of HIV, known as the HIV reservoir, that persists in people taking ART. Researchers are exploring the use of antibodies that target the α4β7 integrin molecule found on the surface of immune-system cells that HIV preferentially infects. Targeting α4β7 integrin can prevent these immune cells from homing to gastrointestinal tissue, a major site of HIV replication and viral reservoir formation early in infection. In a preclinical trial in monkeys infected with SIV, the monkey equivalent of HIV, researchers found that giving ART for 90 days combined with an α4β7 antibody for 23 weeks induced sustained remission of SIV for up to 23 months after treatment. The treatment regimen also almost completely replenished key immune cells that SIV had destroyed, something unachievable with ART alone. NIAID is now conducting an early-phase clinical trial to test a similar treatment regimen in humans.

Research is also ongoing to better understand how some patients experience long periods of ART-free HIV remission. Scientists are studying the case of a nine-year-old South African child diagnosed with HIV at one month of age who received 40 weeks of ART during infancy and has suppressed the virus without ART for 8.5 years. While NIAID is still investigating the long-term effects of early treatment of HIV-infected newborns, this new case of ART-free HIV remission strengthens the hope that a cure of HIV/AIDS is obtainable.

Biodefense and Emerging Infectious Diseases

Outbreaks of new and re-emerging infectious diseases and the increasing prevalence of resistance to antibiotics and other antimicrobial drugs threaten the health of Americans and people worldwide. To address these threats, NIAID conducts and supports research to better understand known and newly identified viruses, bacteria, and other infectious agents, and to inform the development of strategies to diagnose, treat, and prevent infection. NIAID's broad research portfolio and flexible domestic and international infrastructure enable a rapid response to emerging or re-emerging infectious disease threats.

When Ebola virus disease spread quickly through three West African nations, NIAID took an immediate leadership role in the global response and supported the development of some of the most promising vaccine and therapeutic candidates against this deadly infection, building on prior investments in its biodefense research program. NIAID continues to test vaccination strategies to protect against future Ebola virus outbreaks. In 2017, as part of the U.S.-Liberia Partnership for Research on Ebola Virus in Liberia (PREVAIL), NIAID initiated the PREVAC study (PREVAIL V), a Phase II trial of three promising Ebola vaccination strategies. The study will enroll approximately 4,000 individuals to evaluate whether these strategies can safely induce immune responses that are protective against Ebola virus disease.

NIAID also supports research to prevent the spread of vector-borne diseases. A Phase I clinical trial at the NIH Clinical Center is testing the safety of a vaccine called AGS-v. The vaccine is designed to elicit immune responses against proteins in mosquito saliva, thus protecting against numerous devastating human diseases. New infection models have also been developed in ticks and mice to study the biology, transmission of, and countermeasures for tick-borne flaviviruses, such as Powassan virus, which is endemic in the United States, and tick-borne encephalitis.

In 2013, chikungunya, a mosquito-transmitted virus, emerged in the Americas. The virus, which now affects more than 2 million people in over 60 countries, can cause intense joint and muscle pain, fever, and rash. NIAID has helped develop several promising chikungunya vaccine candidates now in clinical testing. One candidate uses virus-like particles to induce protective immune responses. NIAID studies showed that this vaccine candidate may elicit broad antibody responses that protect humans against chikungunya virus. Another vector-borne disease, yellow fever, also recently re-emerged as a major public health concern in parts of Africa and rural Brazil. The existing vaccine is in short supply, and is made in eggs, which limits the ability to ramp-up production quickly in case of an outbreak. This vaccine also can cause adverse side effects that limit its use in some populations, including infants and pregnant women. NIAID is sponsoring a Phase I trial of a novel yellow fever vaccine that may be safe to use in all populations. The NIAID research response to emerging infectious diseases aligns with the NIH Director's theme "Investing in Translational and Clinical Research to Improve Health."

NIAID provides critical tools and preclinical services to help researchers advance discoveries throughout the product development lifecycle. These resources complement efforts supported by other entities, such as the Coalition for Epidemic Preparedness Innovations, to advance promising candidate medical countermeasures into and through clinical testing. NIAID's preclinical services served as a critical resource during the recent Ebola and Zika virus outbreaks, when numerous compounds were rapidly screened for antiviral activity. Several compounds with antiviral activity are being examined further. NIAID is focused particularly on developing a broad-spectrum antiviral drug that could be used to treat a variety of flavivirus infections, including Zika.

Solutions to the growing problem of antimicrobial resistance (AMR) are a top NIAID research priority. NIAID, a member of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, is building on the research agenda it established to focus on key goals of the 2015 *National Action Plan for Combating Antibiotic-Resistant Bacteria*. NIAID solicited proposals for research to help develop novel antibiotic drugs and clinically useful diagnostics for drug-resistant bacteria, as well as vaccines and other preventive strategies that target broad groups of bacteria. A new NIAID initiative will advance the development of candidate vaccines and therapeutics for use against certain pathogens, often deadly, that are prevalent in hospital-associated infections. Together with the HHS Office of the Assistant Secretary for Preparedness and Response, NIAID is conducting a $20 million challenge competition to stimulate the development of new and innovative point-of-need diagnostic tests for antimicrobial-resistant pathogens. The ten best preliminary concepts were selected in March 2017, and proven diagnostics tests will be announced in 2020.

NIAID will continue to focus on basic research, such as systematic evaluations of microbe-host interactions, and its application to product development such as vaccines for pandemic influenza,

multi-drug-resistant tuberculosis, and other high priority pathogens. A top NIAID priority is to support research leading to better therapeutics and vaccines for influenza including the development of a broadly cross-protective or universal vaccine that protects against pandemic and seasonal influenza strains over several years. NIAID will continue to promote basic and clinical research aimed at the development of antimicrobials and vaccines for emerging and re-emerging infectious diseases including antibiotic resistant bacteria. NIAID supports the development of medical countermeasures and new platform technologies against biodefense and emerging infectious disease pathogens and will continue to coordinate with the Biomedical Advanced Research and Development Authority (BARDA) in the advanced development of therapeutics and vaccines.

Program Portrait: Accelerating Vaccine Development with New Technologies

New and re-emerging infectious diseases for which vaccines are not available or have limited efficacy continue to threaten both public health and the economy. NIAID scientists are using translational vaccinology, which incorporates knowledge about immune mechanisms and responses with technological advances, innovative platforms, and cutting-edge approaches to rationally design new and promising vaccine candidates. This area of research uses a coordinated, interdisciplinary approach to speed delivery of an effective vaccine. Current efforts to advance vaccine development include:

- NIAID scientists are leveraging recent advances in structural biology to inform the design of structure-based vaccine candidates. Using this technology, NIAID scientists created a respiratory syncytial virus (RSV) vaccine based on a single, structurally engineered protein from the surface of the virus; this vaccine is currently being tested in a Phase I clinical trial. NIAID also is supporting structure-based vaccine design approaches for vaccines against Ebola virus, group A streptococcus, influenza viruses, hepatitis C virus, and other pathogens.
- Several vaccines under development at the NIAID VRC use a flexible, DNA-based vaccine platform. Pathogen genes are inserted into a small circle of DNA, called a plasmid, for direct delivery into muscle. The same plasmid can be adapted to construct multiple vaccines by inserting a new gene of interest. For example, a plasmid from a previously developed NIAID West Nile virus vaccine candidate was used to develop a DNA-based Zika virus vaccine candidate currently in Phase II/IIb clinical trials.
- Nanoparticle vaccines are an especially versatile and promising new technology. They can envelop viral components into miniscule particles for sustained delivery of a vaccine, which may provide a longer-lasting, more effective immune response. NIAID scientists have leveraged this approach to develop an experimental nanoparticle vaccine featuring the protein ferritin, which self-assembles into nanoparticles, fused genetically with hemagglutinin, the protein found on the surface of the influenza virus. This vaccine has shown protection against lethal influenza infection in animal studies.
- A major goal of NIAID adjuvant research is to develop a “toolbox” of different adjuvants that could be employed to elicit optimal vaccine immunity to different types of infections. NIAID-supported researchers are identifying novel vaccine-enhancing adjuvant candidates using high-throughput screening systems and further developing promising candidates through synthetic chemistry and computer modeling techniques.
- NIAID investigators and grantees employ cutting-edge systems biology technologies to calculate immune responses to pathogens and vaccines, and predict and optimize vaccine targets and adjuvants. This technology informed the development of candidate vaccines for diseases including malaria, Ebola, and influenza.

Infectious and Immunologic Diseases

NIAID leads and supports basic and clinical research to better understand, treat, and prevent infectious diseases and immune-mediated disorders such as asthma, allergy, autoimmune diseases, and transplant rejection. Integral to this research are NIAID efforts to understand the human immune system more fully in the context of health and disease. These immunology studies provide a springboard for developing diagnostics, therapeutics, and vaccines to benefit

people worldwide. NIAID also provides tools, resources and data sharing platforms, such as TrialShare, ImmPort, the Immune Epitope Database, and the OMics Compendia Commons. These resources facilitate analysis of complex data sets from clinical trials and data banks, which are vital for designing and developing vaccines and diagnostics.

Malaria continues to be an urgent global health threat, particularly among children. In FY 2017, NIAID funded 11 International Centers of Excellence for Malaria Research to support research in regions where malaria is endemic. NIAID malaria vaccine researchers and grantees demonstrated that the investigational PfSPZ vaccine provided durable protection against different strains of malaria-causing parasites and provided adults with significant protection throughout the malaria season in Mali. Ongoing research will determine whether changes in the dose and number of immunizations improve vaccine efficacy. Building on promising early-phase clinical trial results, larger clinical trials in malaria-endemic areas are underway to identify an optimal dose and schedule of another experimental vaccine strategy, PfSPZ-CVac. NIAID also supported development of a simple diagnostic test analyzing genetic markers in blood from a finger pinprick to detect drug-resistant parasites and determine the best treatment approach.

In 2015, approximately 1.8 million people died of TB, making it the world's deadliest infectious disease. Although a TB vaccine, BCG, protects against TB-induced meningitis in children, it does not reliably prevent TB-associated lung disease in adults. To advance development of a more effective vaccine, a new NIAID initiative will fund research to better understand the immune responses generated by TB vaccines and by natural infection. In studies in mice, NIAID-supported scientists discovered that BCG vaccine efficacy could be improved by combining it with immune cell–stimulating treatments. Multidrug-resistant TB (MDR-TB) is increasingly prevalent and requires extensive treatment that can cause severe side effects. NIAID-supported researchers have identified potential biomarkers predictive of multidrug resistance, enabling clinicians to target these infections with treatment regimens to prevent resistance. The NIAID-funded HIV/AIDS Clinical Trials Networks are collaborating to launch a study to evaluate a new drug that may prevent the spread of MDR-TB among household members.

Neglected tropical diseases (NTDs) affect more than 1 billion people worldwide, many in the world's poorest communities. NIAID researchers and grantees have gained insight into one such devastating illness, river blindness, caused by the parasite *Onchocerca volvulus.* By sequencing the genome of *O. volvulus* samples found in three African nations, they identified proteins that could be targeted with existing drugs or may be used to develop new treatments. NIAID-funded researchers also discovered new treatment targets for leishmaniasis, a parasitic disease transmitted by sand flies and marked by severe skin ulcers that take months or years to heal. Existing drugs that act on some of these targets could be repurposed to treat leishmaniasis. In FY 2017, NIAID renewed support for the multidisciplinary Tropical Medicine Research Centers, located in regions directly affected by NTDs. These centers will research and implement life-saving treatments and conduct firsthand studies of how NTDs develop and spread.

Lyme disease can be difficult to diagnose. If untreated, it may damage the heart, nervous system, and musculoskeletal system. Research on Lyme disease pathogenesis, prevention, and improved diagnosis is an important NIAID priority. NIAID-supported advances in diagnosis

include a rapid, sensitive, point-of-care test that shows promise for detecting early-stage Lyme disease. Other advances such as detecting serum proteins that may distinguish between early- and late-stage Lyme disease and identifying clinical differences among various forms of arthritis that can occur after infection may help clinical management of disease.

NIAID-funded research focuses on reducing the burden of allergy and asthma through studies on causation, prevention, and treatment. Inner-City Asthma Consortium (ICAC) researchers recently found that children who are exposed to mouse, cat, or cockroach allergens during infancy have a lower risk of developing asthma by age seven years. By contrast, ICAC researchers found that older children who already have asthma and were exposed to airborne mouse allergens at school had increased asthma symptoms and reduced lung function. These studies can inform prevention strategies to lower the risk of developing asthma and treatment strategies to ameliorate symptoms in children with established disease. NIAID renewed the Food Allergy Research Consortium in FY 2017 to sustain the quest for food allergy prevention and treatment strategies. Based on results of the Learning Early About Peanut (LEAP) trial, NIAID published new clinical guidelines[5] for preventing peanut allergy and is developing clinical trials for the prevention of egg and milk allergies.

The FY 2019 IID research plan continues to advance NIAID's long-range research priorities and is carefully aligned to support key research activities including basic and clinical research aimed at the development of countermeasures such as therapeutics, vaccines and diagnostics for emerging and re-emerging infectious diseases, including antibiotic resistant bacteria. Funding will also continue to reflect NIAID's commitment and long-term interest in fundamental immunology and support research on organ transplantation, autoimmune diseases, asthma and other allergic diseases.

[5] Togias A., Cooper S.F., Acebal M.L., et al. Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. *J Allergy Clin Immunol*. 2017 Jan;139(1):29-44.

Program Portrait: Advances in Primary Immune Deficiency Diseases

Primary immune deficiency diseases (PIDDs) are a group of rare, chronic genetic disorders that prevent the body from developing normal immune responses. In the United States, PIDDs affect approximately 500,000 people. These debilitating, costly, and frequently fatal disorders predispose people to recurrent infections, cancer, chronic inflammation, autoimmune disorders, and allergic disease. PIDDs often run in families and can cause significant financial hardship and emotional distress.

Using increasingly sophisticated genetic techniques, scientists continue to identify new PIDDs and gain insights into their causes and possible treatments—and in the process, uncover new details of normal immune function and synergize with ongoing basic research. One recent example built upon NIAID-supported research showing that mice lacking the protein MDA5 are unusually susceptible to viral infection and post-viral pulmonary inflammation. NIAID scientists and their colleagues discovered a disorder, MDA5 deficiency, in a young child, that markedly increases susceptibility to infection by human rhinoviruses (HRVs)—the main causes of the common cold. This work not only helped the affected child, but also revealed an important mechanism the immune system uses to respond to HRVs. These findings could also inform new strategies for treating patients with severe HRV complications, which can lead to hospitalization, disability, and even death, especially in infants and the elderly.

In another study, researchers discovered that mutations in the *CD55* gene cause a life-threatening gut condition, CHAPLE disease, which leads to hyperactivity of a group of immune system proteins called complement. When the researchers exposed patient immune cells to eculizumab, a therapeutic antibody approved to treat another rare condition, complement production decreased. Future work will test the antibody in people with CHAPLE disease in hopes that it could be the first effective treatment.

For these and many other PIDDs, there are no cures available, and in many cases, no treatments. However, research conducted by NIAID-funded investigators has led to a practice-changing diagnostic test and treatment strategy. Widespread adoption of newborn screening for severe combined immune deficiency (SCID), a rare genetic disorder, has allowed prompt treatment that increases the survival rate of affected infants. Hematopoietic stem cell transplant for SCID before 3.5 months of life in the absence of infection has resulted in greatly improved survival rates, and these infants are being followed into early adulthood. However, to avoid issues such as limited donor availability and the risk of serious transplant-related morbidity, NIAID is supporting work with the potential to cure PIDDs by replacing or repairing defective genes in the patient's own cells. For example, NIAID is supporting studies in blood-forming cells based on the gene-editing tool CRISPR-Cas9 that precisely targets and corrects disease-causing mutations.

Intramural Research Program (IRP)

Complementing the NIAID extramural research program, NIAID scientists in the IRP lead efforts to expand our knowledge of healthy immune system function, define mechanisms that underlie immunologic diseases, understand the biology of infectious agents, and elucidate the host response to infection. NIAID infectious disease experts employ state-of-the-art infrastructure to translate basic discoveries rapidly into new diagnostics, therapies, and prevention strategies for infectious and allergic diseases.

The IRP consists of three components: 1) the Division of Intramural Research, which comprises more than 110 principal investigators in Maryland and at the Rocky Mountain Laboratories in Montana who lead a wide range of basic, translational, and clinical research efforts in infectious diseases, allergy, and immunology; 2) the Vaccine Research Center, which applies fundamental advances in immunology, virology, and vaccine science to discover and develop new and improved vaccines, including several mentioned above (for example, Zika and chikungunya); and 3) the Division of Clinical Research, which facilitates efficient and effective NIAID clinical research programs in the United States and internationally, such as the U.S.-Liberia PREVAIL partnership described above. The IRP also leverages its longstanding domestic and international

partnerships to respond quickly to emerging infectious threats such as Zika virus and Ebola virus.

IRP scientists are leaders in identifying genetic links to allergic and immunologic disorders and devising new treatments for them. For example, one recent study found that mutations in a gene called *CARD11* can lead to the allergic skin disease atopic dermatitis (eczema). Another study found that inheriting too many copies of the *TPSAB1* gene can lead to an array of symptoms including dizziness and lightheadedness, skin flushing and itching, gastrointestinal complaints, chronic pain, and bone and joint problems. Such genetic links have helped scientists develop treatment strategies tailored more specifically to individuals.

Another IRP strength is the ability to perform high-risk, high-reward studies, for instance, efforts to advance toward a "universal" influenza vaccine, and to develop a candidate vaccine HSV529 against herpes simplex virus-2 (HSV-2). HSV-1 or HSV-2 infections afflict most of the global population and cause problems ranging from oral or genital lesions to serious eye conditions that can lead to blindness. In addition, neonatal infections can result in mortality, developmental delays, or neurological issues. IRP scientists have recently identified groups of proteins essential for promoting initial HSV infection and reactivation from the dormant or latent state. These findings may provide novel targets for developing therapeutics for HSV. IRP scientists also identified a mechanism to enhance the normal antiviral response to HSV and other viruses. This approach could lead to the development of broad-spectrum antiviral therapies.

The extensive IRP advances many facets of basic biomedical research—a focus that reflects the NIH Director's theme "Supporting Basic Research to Drive New Understanding of Health and Disease in Living Systems."

The FY 2019 Intramural Research plan supports critical long-range research priorities of NIAID with funding carefully aligned to support key research activities. These include the continued support for all aspects of research on infectious diseases such as AIDS, malaria, and influenza, including the causative agent, vectors and the human host. In addition, we are developing countermeasures against bioterrorism through basic research and our strong clinical research component allowing key lab discoveries to be rapidly translated into methods to prevent, diagnose, or treat disease.

Research Management and Support (RMS)
RMS activities provide administrative, budgetary, logistical, and scientific support in the review, award, and monitoring of research grants, training awards, and research and development contracts. RMS activities include strategic planning, coordination, and evaluation of Institute programs, as well as regulatory compliance, international coordination, and liaison with other Federal agencies, Congress, and the public.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Detail of Full-Time Equivalent Employment (FTE)

OFFICE/DIVISION	FY 2017 Final			FY 2018 Annualized CR			FY 2019 President's Budget		
	Civilian	Military	Total	Civilian	Military	Total	Civilian	Military	Total
Division of Acquired Immunodeficiency									
Direct:	141	9	150	141	9	150	141	9	150
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	141	9	150	141	9	150	141	9	150
Division of Allergy, Immunology, and Transplantation									
Direct:	93	-	93	93	-	93	93	-	93
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	93	-	93	93	-	93	93	-	93
Division of Clinical Research									
Direct:	84	12	96	84	12	96	84	12	96
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	84	12	96	84	12	96	84	12	96
Division of Extramural Activities									
Direct:	224	-	224	228	-	228	228	-	228
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	224	-	224	228	-	228	228	-	228
Division of Intramural Research									
Direct:	674	13	687	674	13	687	674	13	687
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	674	13	687	674	13	687	674	13	687
Division of Microbiology and Infectious Diseases									
Direct:	174	7	181	174	7	181	174	7	181
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	174	7	181	174	7	181	174	7	181
Office of the Director									
Direct:	423	2	425	423	2	425	423	2	425
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	423	2	425	423	2	425	423	2	425
Vaccine Research Center									
Direct:	103	-	103	103	-	103	103	-	103
Reimbursable:	-	-	-	-	-	-	-	-	-
Total:	103	-	103	103	-	103	103	-	103
Total	1,916	43	1,959	1,920	43	1,963	1,920	43	1,963
Includes FTEs whose payroll obligations are supported by the NIH Common Fund.									
FTEs supported by funds from Cooperative Research and Development Agreements.	0	0	0	0	0	0	0	0	0

FISCAL YEAR	Average GS Grade
2015	12.3
2016	12.4
2017	12.5
2018	12.5
2019	12.5

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Detail of Positions[1]

GRADE	FY 2017 Final	FY 2018 Annualized CR	FY 2019 President's Budget
Total, ES Positions	2	2	2
Total, ES Salary	374,000	381,106	382,935
GM/GS-15	164	164	164
GM/GS-14	429	429	429
GM/GS-13	344	345	345
GS-12	223	225	225
GS-11	129	129	129
GS-10	1	1	1
GS-9	69	70	70
GS-8	29	29	29
GS-7	52	52	52
GS-6	9	9	9
GS-5	8	8	8
GS-4	7	7	7
GS-3	9	9	9
GS-2	2	2	2
GS-1	1	1	1
Subtotal	1,476	1,480	1,480
Grades established by Act of July 1, 1944 (42 U.S.C. 207)	0	0	0
Assistant Surgeon General	1	1	1
Director Grade	18	18	18
Senior Grade	9	9	9
Full Grade	8	8	8
Senior Assistant Grade	7	7	7
Assistant Grade	1	1	1
Subtotal	44	44	44
Ungraded	453	453	453
Total permanent positions	1,509	1,509	1,509
Total positions, end of year	1,975	1,979	1,979
Total full-time equivalent (FTE) employment, end of year	1,959	1,963	1,963
Average ES salary	187,000	190,553	191,468
Average GM/GS grade	12.5	12.5	12.5
Average GM/GS salary	108,986	111,056	111,589

[1] Includes FTEs whose payroll obligations are supported by the NIH Common Fund.