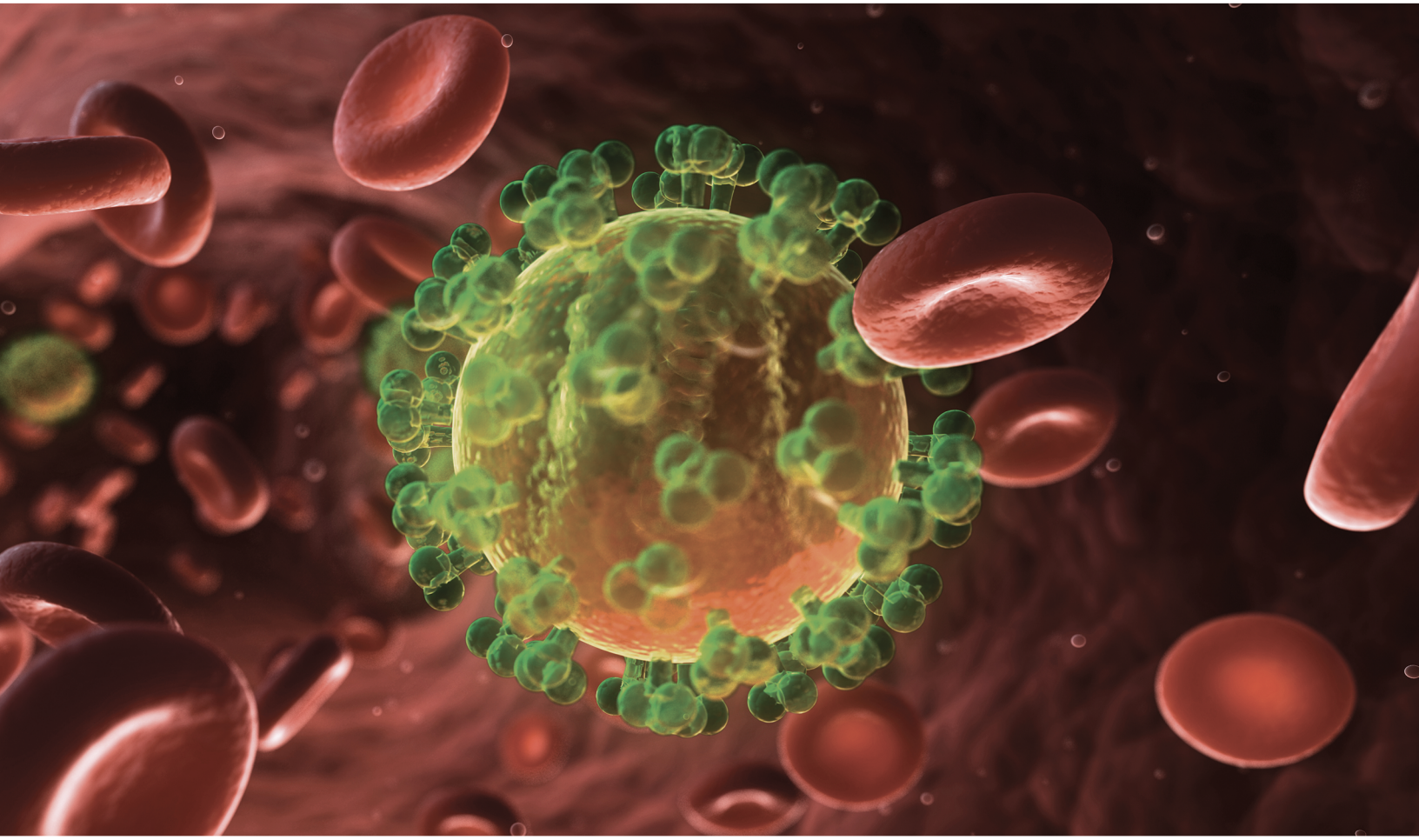


Fiscal Year 2017

Trans-NIH AIDS

By-Pass Budget Estimate

Prepared by the Office of AIDS Research

Table of Contents

Legislative Mandate 1

Introduction 2

The Global AIDS Pandemic 3

The HIV/AIDS Epidemic in the United States 3

HIV Care Continuum in the United States 4

Key Research Priorities for FY 2017 5

Annual Trans-NIH AIDS Research Budget 6

- FY 2017 Trans-NIH AIDS By-Pass Budget 6
- FY 2017 Trans-NIH AIDS Research By-Pass Budget, by Overarching Priorities 7
- FY 2017 Trans-NIH AIDS Research By-Pass Budget, by Scientific Area of Emphasis 7

The Office of AIDS Research and the Trans-NIH HIV/AIDS Research Program 8

Global Impact of HIV/AIDS Research 10

Benefits of HIV/AIDS Research 11

Conclusion 12

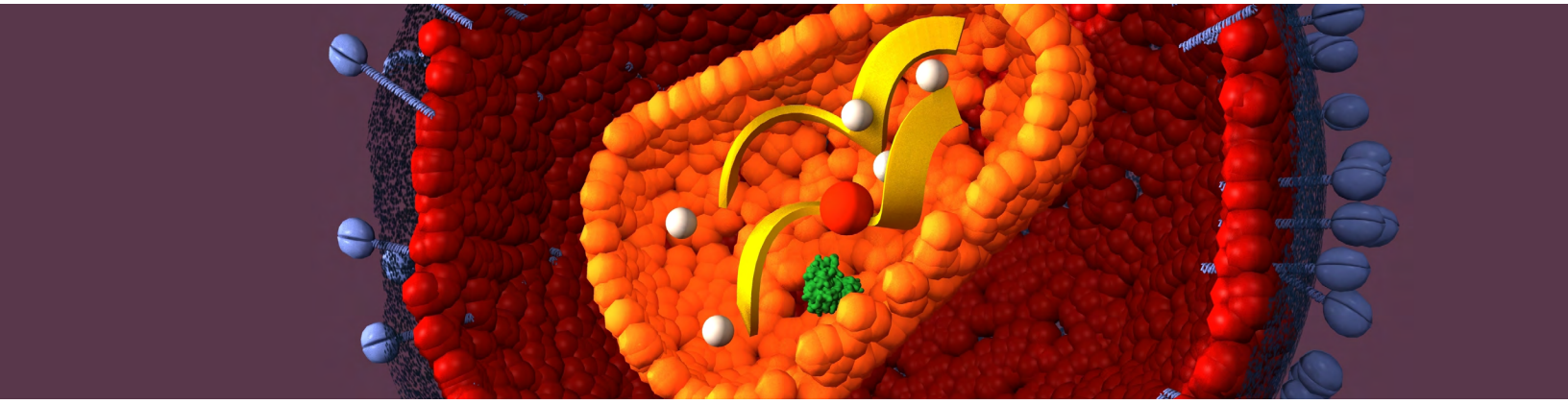
Appendix 1: FY 2017 Trans-NIH Plan for HIV-Related Research

Legislative Mandate

Section 2353 of the Public Health Service Act requires that "the Director of the Office of AIDS Research (OAR) establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health."

It also requires that the OAR Director "prepare and submit directly to the President, for review and transmittal to the Congress, a budget estimate for carrying out the Plan for the fiscal year, after reasonable opportunity for comment (but without change) by the Secretary, the Director of the National Institutes of Health, and the Advisory Council...."

That budget "shall estimate the amounts necessary for the agencies of the National Institutes of Health to carry out all AIDS activities determined by the Director of the Office to be appropriate, without regard to the probability that such amounts will be appropriated."



Introduction

In accordance with Section 2353 of the Public Health Service Act, the National Institutes of Health (NIH) Office of AIDS Research (OAR), a component of the NIH Office of the Director, has developed this *Fiscal Year 2017 Trans-NIH AIDS Research By-Pass Budget Estimate*. OAR is the only entity at the NIH that sets trans-NIH HIV/AIDS research priorities through a strategic plan and builds a budget based on those priorities.

We have made extraordinary strides in HIV/AIDS research, including the development, use, and implementation of biomedical and behavioral modalities for HIV/AIDS diagnosis, prevention, and treatment. A great deal more is yet to be done in the United States and internationally. The need for a safe and effective vaccine, strategies for achieving a cure, and the reduction of health disparities among various vulnerable populations with respect to HIV/AIDS outcomes are critical.

Recent outbreaks of HIV infection through injection drug use in Indiana are a harsh reminder that even in the United States, the epidemic still remains a threat. Furthermore, a recent article about disease outcomes in San Francisco reported that "HIV-related opportunistic infections continue to occur and that patients still die at alarming rates during the early years after their first AIDS-related opportunistic infection is recognized—a 35 percent mortality rate within 5 years of diagnosis of the initial AIDS-defining opportunistic infection leaves considerable room for improvement." In San Francisco, a city with a wide variety of programs to prevent and treat HIV infection, only 65 percent of patients are surviving 5 years after diagnosis of initial opportunistic infection.

Recent reports continue to show that HIV-related comorbidities and coinfections are increasing among HIV-infected individuals, including AIDS-related cancers, cardiovascular complications, neurological disorders, neurocognitive impairment, and metabolic abnormalities. NIH-funded studies provide evidence that HIV-associated comorbidities remain prevalent despite antiretroviral therapy. These studies also demonstrate that early asymptomatic neurocognitive impairment and other comorbidities confer an increased risk and faster development of functional/symptomatic decline in individuals with HIV disease progression.

The NIH HIV/AIDS research program—conducted and supported by nearly all of the NIH Institutes and Centers (ICs), with trans-NIH coordination and management by OAR—has been one of the NIH's most successful investments. It has resulted in profound discoveries that have led to improvements in care for individuals with HIV/AIDS, with crossover benefits to patients with many other diseases. The NIH must continue to search for critical strategies to prevent, treat, and eventually cure HIV/AIDS.

This By-Pass budget is based solely on current scientific opportunities and new overarching priorities that were defined in the NIH Director's Statement of August 12, 2015, and are reflected in the FY 2017 Trans-NIH Plan for HIV-Related Research (Appendix 1). The NIH will continue to build on the scientific advances that have been gained to address the unprecedented scientific opportunities that we now face to develop a safe and effective AIDS vaccine and a cure for AIDS and lead to an AIDS-free generation and an end to the AIDS pandemic.

With sincere appreciation,
Robert W. Eisinger, Ph.D.
NIH Acting Associate Director for AIDS Research and
Acting Director, Office of AIDS Research

The Global AIDS Pandemic

AIDS is an infectious disease that is continuing to spread, devastating communities and crucial socioeconomic infrastructures around the world. The AIDS pandemic has been declared a threat to our national security, and the United Nations General Assembly declared it "a global emergency and one of the most formidable challenges to human life and dignity...which undermines social and economic development throughout the world and affects all levels of society—national, community, family and the individual." According to the latest UNAIDS statistics reported in 2015 (in summary)—

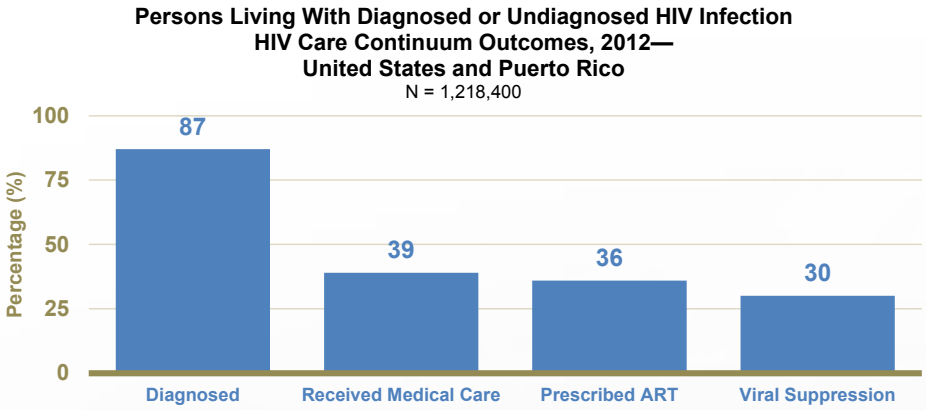
- 36.9 million people globally were living with HIV.
- 2 million people became newly infected with HIV.
- 1.2 million people died from AIDS-related illnesses.
- 15.8 million people were accessing antiretroviral therapy.
- Tuberculosis-related deaths in people living with HIV have fallen by 32 percent since 2004. However, tuberculosis remains the leading cause of death among people living with HIV.
- 73 percent of pregnant women living with HIV had access to antiretroviral medicines to prevent transmission of HIV to their babies in 2014; new HIV infections among children were reduced by 58 percent from 2000 to 2014.

The HIV/AIDS Epidemic in the United States

According to the latest Centers for Disease Control and Prevention (CDC) statistics in 2014 (in summary)—

- Roughly 1.2 million people in the United States were living with HIV.
- Although an estimated 44,073 individuals were diagnosed with HIV, new HIV infections have remained at about 50,000 cases per year for more than a decade.
- Men who have sex with men continue to be the group most heavily affected by HIV in the United States, accounting for nearly 67 percent of all persons with HIV diagnosed in 2014.
- Although African Americans represent approximately 13 percent of the total U.S. population, they accounted for almost one-half (44 percent) of all HIV diagnoses in 2014. Similarly, Latino men and women accounted for 23 percent of all new HIV diagnoses, while representing only 17 percent of the population.
- Southern states account for an estimated 44 percent of all people living with an HIV diagnosis, despite making up roughly one-third (37 percent) of the national population. In addition, people living with HIV in the South are less likely to be aware of their infection than those living in other U.S. regions.
- Only 30 percent of HIV-infected individuals in the United States are virally suppressed (the point at which the virus is under control, and a person can remain healthy and reduce the risk of transmission)—a proportion that is even lower among blacks (29 percent) and young people ages 25–34 (23 percent).

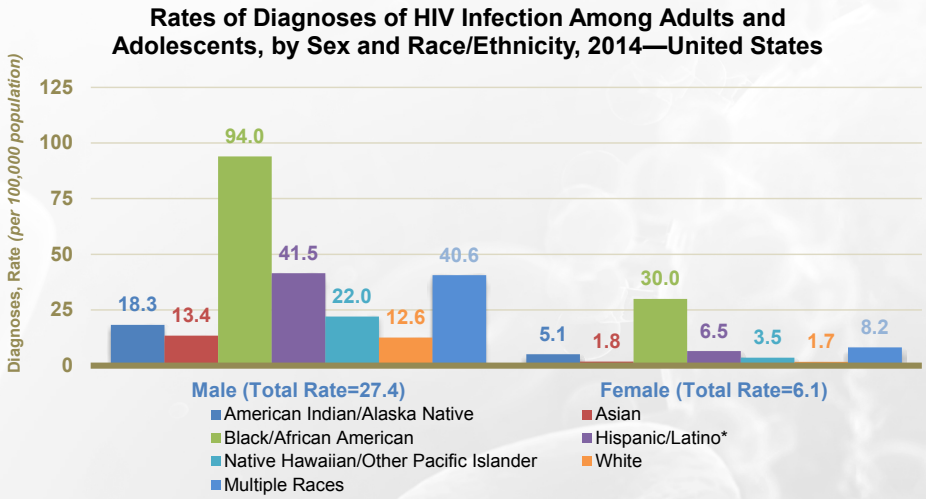
HIV Care Continuum in the United States



National HIV Surveillance System: Estimated number of persons age ≥13 years living with diagnosed or undiagnosed HIV infection (prevalence) in the United States at the end of the specified year. The estimated number of persons with diagnosed HIV infection was calculated as part of the overall prevalence estimate.

Medical Monitoring Project: Estimated number of persons age ≥18 years who received HIV medical care during January to April of the specified year, were prescribed antiretroviral treatment (ART), or whose most recent viral load in the previous year was undetectable or < 200 copies/mL—United States and Puerto Rico.

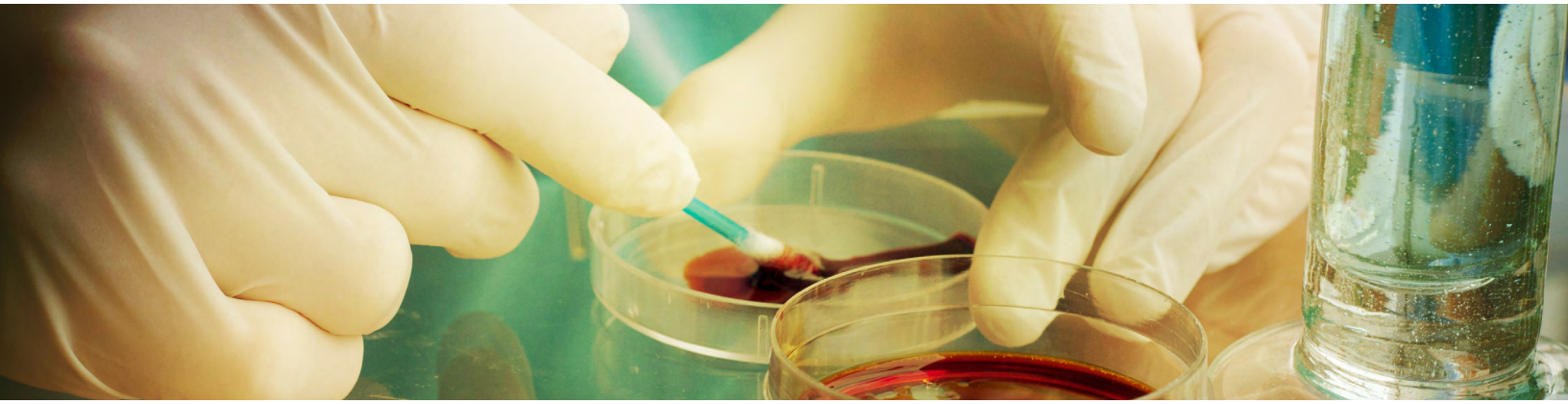
Source: Centers for Disease Control and Prevention



Note: Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. All displayed data have been statistically adjusted to account for reporting delays, but not for incomplete reporting.

*Hispanics/Latinos can be of any race.

Source: Centers for Disease Control and Prevention



Key Research Priorities for FY 2017

The following overarching HIV/AIDS research priorities have been identified:

- **Reduce the incidence of HIV/AIDS, including:** developing and testing promising vaccine, microbicide and pre-exposure prophylaxis candidates and novel methods of delivery, especially those with potential to mitigate adherence issues; and developing, testing, and studying strategies and the implementation of strategies to improve HIV testing, and entry, and maintenance in prevention care and services.
- **Next generation of HIV therapies with better safety and ease of use, including:** developing and testing HIV treatments that are less toxic, longer acting, have fewer side effects and complications, and easier to take and adhere to than current regimens; implementing research to understand how best to initiate treatment as soon as an HIV diagnosis has been made, improving engagement and retention in care; and achieving and maintaining optimal prevention and treatment responses.
- **Research toward a cure, including:** developing novel approaches and strategies to identify and eliminate viral reservoirs that could lead toward a cure or lifelong remission of HIV infection, including studies of viral persistence, latency, reactivation, and eradication.
- **HIV-associated coinfections, comorbidities, and complications, including:** addressing the impact of HIV-associated comorbidities, including tuberculosis, malignancies, cardiovascular, neurological, and metabolic complications; and premature aging associated with long-term HIV disease and antiretroviral therapy.
- **Crosscutting areas:** Basic research, health disparities, and training, including:
    - **Basic Research:** understanding the basic biology of HIV transmission and pathogenesis; immune dysfunction and chronic inflammation; host microbiome and host and viral genetics that impact susceptibility to infection and disease outcomes; and other fundamental issues that underpin the development of high-priority HIV prevention, cure, comorbidities, and treatment strategies.
    - **Research to Reduce Health Disparities** in the incidence of new HIV infections or in treatment outcomes of those living with HIV/AIDS.
    - **Research Training** of the workforce required to conduct high-priority HIV/AIDS or HIV/AIDS-related research.

Annual Trans-NIH AIDS Research Budget

The OAR is mandated to develop an annual trans-NIH research budget in partnership with the ICs. The budget is explicitly tied to the new overarching HIV/AIDS research priorities and the areas of emphasis of the Strategic Plan. The law provides that the OAR "shall receive directly from the President and Director of the Office of Management and Budget all funds available for AIDS activities of the NIH" for allocation to the ICs in accordance with the Strategic Plan.

The ICs submit their AIDS-related research budget requests to the OAR, presenting proposed new, expanded, or recompeting program initiatives, aligned to the new overarching priorities and scientific areas of emphasis. The OAR reviews the IC initiatives in relation to the priorities, and other IC submissions to eliminate redundancy and ensure cross-IC collaboration. The unique budget authorities allow the OAR to build each IC budget from the commitment base, rather than from the previous year's appropriation.

FY 2017 Trans-NIH AIDS By-Pass Budget

The OAR is authorized to allocate all funds associated with this area of research across the NIH. The total funding for HIV/AIDS research includes both extramural and intramural research (including research management support, a management fund, and a service and supply fund), buildings and facilities, research training, and program evaluation. This budget request supports a comprehensive program that includes basic, clinical, behavioral, social science, and translational research on HIV and its associated malignancies, coinfections such as tuberculosis and hepatitis C, comorbidities, and other complications. The total funding for HIV/AIDS research is therefore not comparable to the NIH spending reported for other diseases.

The OAR's legislative authority requires the development of this By-Pass budget estimate based solely on the current scientific opportunities and the commitment and urgent need to support the new overarching research priorities defined in the NIH Director's Statement, including to develop a vaccine and cure for AIDS and, ultimately, an end to the AIDS pandemic. (*www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-efforts-focus-research-end-aids-pandemic*)

This By-Pass budget request—

- Addresses critical scientific needs;
- Capitalizes on emerging scientific opportunities by providing additional funds for newly identified areas of investigation; and
- Establishes the research foundation necessary to implement the major goals of the President's National HIV/AIDS Strategy 2020 and the accompanying Federal Action Plan.

To address the new NIH overarching HIV/AIDS research priorities, the Fiscal Year (FY) 2017 By-Pass budget estimate for the trans-NIH AIDS research program is $3,225,066,000, an increase of $225,005,000 (or 7.5%) more than the FY 2016 enacted level. This request reflects the reallocation of resources to address the evolving clinical profile of the epidemic and meet the highest priorities identified through OAR's trans-NIH strategic planning, priority-setting, portfolio analysis, and budget processes.

FY 2017 Trans-NIH HIV/AIDS Research By-Pass Budget, by Overarching Priorities (U.S. dollars in thousands)

Overarching Priority	FY 2015 Actual	FY 2016 Enacted	FY 2017 By-Pass	FY 2017 +/- FY 2016	Change
Reducing Incidence of HIV/AIDS	$1,015,701	$1,061,313	$1,172,368	$111,055	10.5%
Next Generation Therapies	493,780	467,502	491,616	24,114	5.2%
Develop a Cure for HIV/AIDS	161,045	187,280	203,879	16,599	8.9%
Improve Treatments for HIV-Associated Comorbidities and Coinfections	585,909	586,243	619,064	32,821	5.6%
Crosscutting—Basic Research, Health Disparities, and Reseach Training	743,626	697,723	738,139	40,416	5.8%
TOTAL	**$3,000,061**	**$3,000,061**	**$3,225,066**	**$225,005**	**7.5%**

FY 2017 Trans-NIH HIV/AIDS Research By-Pass Budget, by Scientific Area of Emphasis (U.S. dollars in thousands)

Area of Emphasis	FY 2015 Actual	FY 2016 Enacted	FY 2017 By-Pass	FY 2017 +/- FY 2016	Change
Vaccines	$534,987	$552,803	$641,316	$88,513	16.0%
HIV Microbicides	106,104	109,656	115,879	6,223	5.7%
Behavioral and Social Science	411,359	421,669	440,669	19,000	4.5%
Etiology and Pathogenesis	597,518	602,180	638,039	35,859	6.0%
Therapeutics					
Therapeutics as Prevention	71,698	79,775	83,273	3,498	4.4%
Drug Discovery, Development, and Treatment	595,543	570,534	601,902	31,368	5.5%
TOTAL, Therapeutics	667,241	650,309	685,175	34,866	5.4%
Toward a Cure [1]	161,045	187,280	203,879	16,599	8.9%
Natural History and Epidemiology	232,078	237,440	248,655	11,215	4.7%
Training, Infrastructure, and Capacity Building	249,376	199,973	210,586	10,613	5.3%
Information Dissemination	40,353	38,751	40,868	2,117	5.5%
TOTAL	**$3,000,061**	**$3,000,061**	**$3,225,066**	**$225,005**	**7.5%**

[1]Beginning in FY 2017, Toward a Cure will be a separate activity. Dollars for Toward a Cure were previously included within other science areas, such as Therapeutics, Etiology and Pathogenesis, and Vaccines. The FY 2015 and FY 2016 amounts are comparable budget figures.

The Office of AIDS Research and the Trans-NIH HIV/AIDS Research Program

The NIH HIV/AIDS research program is coordinated and managed by the OAR, with responsibility for HIV/AIDS-related research supported by almost every NIH IC. OAR coordinates the scientific, budgetary, and policy elements of this diverse trans-NIH research program. OAR plans and coordinates NIH HIV/AIDS research through development of the annual Trans-NIH Plan for HIV-Related Research, which identifies the overarching research priorities. This process involves scientists from across the NIH and other Federal agencies, nongovernment experts, and community constituency groups. The Plan also serves as the framework for developing the annual trans-NIH HIV/AIDS research budget to ensure that research dollars are invested in the highest priority areas of scientific opportunity that will lead to new tools ending the HIV/AIDS pandemic, developing a safe and effective AIDS vaccine, developing a cure, and achieving an AIDS-free generation.

As required by law, the Director of the OAR and the Director of the NIH together determine the total allocation of AIDS research dollars. The OAR determines each IC's AIDS research allocation based on the Trans-NIH Plan for HIV-Related Research, scientific opportunities, the evolving clinical profile of the epidemic, and the IC's capacity to absorb and expend resources for the most meritorious science. The allocations are not based on a formula. This process reduces redundancy, promotes harmonization, and ensures cross-Institute collaboration. The NIH investment in HIV/AIDS research has produced groundbreaking scientific advances that continue to provide a critical foundation of knowledge, tools, and strategies for achieving the goals of the President's National HIV/AIDS Strategy.

The challenges posed by HIV/AIDS exceed the mission or expertise of any single NIH IC. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation. Consequently, nearly every NIH IC conducts or supports HIV/AIDS research within its mission, allowing the breadth of critical science and expertise to remain in the individual IC. Examples of individual IC research programs include the following:

- The National Institute of Allergy and Infectious Diseases supports a comprehensive research portfolio aimed at: (1) basic research on HIV pathogenesis and the immunologic response to HIV; (2) halting the spread of HIV transmission through effective and acceptable prevention strategies, including a preventive vaccine and microbicides; (3) treatment of HIV infection and strategies leading to a cure for HIV/AIDS; and (4) development and testing of prevention and treatment strategies for HIV-associated coinfections, comorbidities, and other complications.

- The National Cancer Institute supports important clinical research on AIDS-defining and non-AIDS defining cancers.

- The National Institute of Neurological Disorders and Stroke funds research demonstrating that the brain is an important reservoir of HIV infection and that changes in the brain can be detected as early as 4 months after infection.

- The National Heart, Lung, and Blood Institute sponsors researchers who investigate the high risk of cardiovascular and metabolic complications in HIV-infected individuals.

- The National Institute on Aging supports studies that identify issues of premature aging among HIV-infected individuals.
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development leads clinical trials to improve the effectiveness of strategies to prevent mother-to-child transmission and clinical studies on HIV prevention and treatment among adolescents.
- The National Institute of General Medical Sciences supports research to define the structural characterization of HIV enzymes and viral proteins, which has been instrumental in the development of antiretroviral drug therapies, including protease inhibitors.
- The Fogarty International Center supports critical international training and infrastructure programs.
- The National Library of Medicine supports the resources of *AIDSInfo*, which offers access to the latest federally approved HIV/AIDS medical practice guidelines (developed by guidelines panels under the auspices of the OAR Advisory Council); HIV treatment and prevention clinical trials; and other research information for researchers, health care providers, and people affected by HIV/AIDS. These resources benefit not only people within the United States, but also millions of people globally.

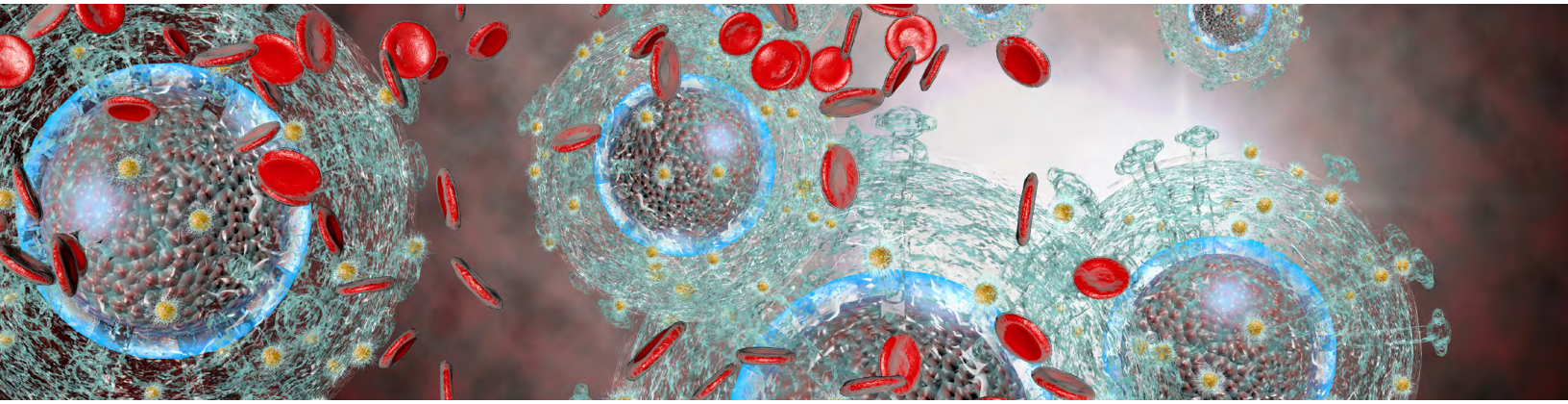
This multifaceted research portfolio demands an unprecedented level of scientific coordination and management of research funds. The OAR coordinates and manages the scientific, budgetary, evaluation, and policy elements of this complex, comprehensive, multidisciplinary, and global research program, functioning as an "institute without walls."

Utilizing its legislative authorities, the OAR has established comprehensive trans-NIH planning, portfolio analysis, and budgeting processes to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that research resources are invested effectively and efficiently.

Global Impact of HIV/AIDS Research

Research to address the global AIDS pandemic is essential. Since the early days of the pandemic, the NIH has supported research in countries significantly affected by HIV/AIDS, beginning in 1983 with a research project in Haiti. The NIH international HIV/AIDS research portfolio currently includes projects in more than 100 countries. HIV/AIDS research represents the largest component of the total NIH global research investment. Studies are designed so that the research is conducted in accordance with the highest bioethical and biomedical standards and that the results are relevant for both the host nation and the United States.

Implementation studies are critical to translating clinical trial results into community-based interventions that can be operational and sustainable in international settings. These programs also enhance the research infrastructure and training of in-country scientists and health care providers. New collaborations have been designed to improve both medical and nursing education as a mechanism to build a cadre of global health leaders. Most of these grants and contracts are awarded to U.S.-based investigators to conduct research in collaboration with in-country scientists; some are awarded directly to investigators in international scientific, academic, or medical institutions.



Benefits of HIV/AIDS Research

It is important to note that the NIH investment in HIV/AIDS research has resulted in critical scientific accomplishments that not only have benefited the roughly 36.9 million HIV-infected individuals around the world, but also have contributed knowledge to the prevention, diagnosis, and treatment of many other diseases and health conditions.

NIH-sponsored HIV/AIDS research is helping to unravel the mysteries surrounding other diseases because of the pace of discovery and the unique nature of HIV (i.e., the way the virus enters a cell, causes infection, affects every organ system, and involves a broad range of opportunistic infections, comorbidities, cancers, and other complications). HIV/AIDS research broadens the overall understanding of immunology, virology, microbiology, molecular biology, and genetics. The study of drugs to treat HIV infection and its complications also has helped to establish new approaches for the design and conduct of more rapid clinical studies, as well as those that address the special recruitment requirements of women, minorities, and other underrepresented populations. In addition to learning more about the special recruitment requirements of these populations, the investment in behavioral and social sciences research has provided effective strategies for intervening in other diseases modified by individual behaviors.

New investments in HIV/AIDS research will continue to accelerate biomedical advances and breakthroughs that will have profound benefits far beyond the AIDS pandemic, such as the following:

- AIDS immunology and biology research also has informed the understanding of inflammation and aging.
- HIV/AIDS research continues to make discoveries that can be applied to other infectious, malignant, neurologic, autoimmune, and metabolic diseases, as well as to the complex issues of aging.
- Research on HIV-associated neurologic and neurocognitive manifestations ultimately may benefit millions of patients with Alzheimer's disease and other aging and dementia conditions.
- HIV/AIDS treatment research has led to more effective drugs for multiple bacterial, mycobacterial, and fungal diseases and has fostered significant improvements in drug design and delivery technologies that can improve adherence. It also has led to the development of curative regimens for hepatitis C, which affects about 150 million people globally.
- HIV/AIDS research has led to the development of new models to test treatments for other diseases in faster, more efficient, and more inclusive clinical trials.
- Drugs developed to prevent and treat HIV-associated opportunistic infections now benefit patients undergoing cancer chemotherapy and the more than 28,000 Americans who receive an organ transplant each year.
- HIV/AIDS research has advanced our understanding of the relationship between viruses and cancer. New research has demonstrated that a drug approved for treating HIV disease may slow the progression of prostate cancer.
- Basic HIV transmission and pathogenesis studies have significant implications for preventing or limiting future pandemics as observed in the most recent Ebola and Zika virus outbreaks.

Conclusion

The NIH's investment in HIV/AIDS research has produced groundbreaking scientific advances that have benefited not only HIV-infected individuals, but also those with other diseases. Looking ahead, there are unprecedented scientific opportunities that will lead to better, more effective, and affordable prevention and treatment regimens.

This By-Pass budget request represents the collective professional judgment of scientific experts from around the country and the world on the highest priority areas of scientific opportunity and investment of NIH AIDS resources. The NIH's continued leadership and commitment to build on these scientific advances are essential to successfully develop a safe and effective AIDS vaccine, develop strategies to cure AIDS, and, ultimately, achieve an AIDS-free generation and an end to the AIDS pandemic. This FY 2017 AIDS By-Pass Budget request provides the essential resources to achieve these overarching priorities.

Appendix 1: FY 2017 Trans-NIH Plan for HIV-Related Research

FY **2017**

Trans-NIH Plan for HIV-Related Research

NIH

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

Dedicated to the Memory of William E. Paul, M.D.

(1936-2015)

Dr. Paul was a leader in the field of immunology and spent more than 30 years at the NIH. As Director of the NIH Office of AIDS Research (OAR) from 1994 to 1997, he refocused HIV/AIDS research with a priority on basic and vaccine research. He championed the establishment of the NIH Vaccine Research Center. The NIH and the global research community mourn his loss, but his legacy remains.

Table of Contents

Foreword ii

Overarching HIV/AIDS Research Priorities for AIDS Funding 1

Reducing the Incidence of HIV/AIDS 2

Next Generation Therapies for HIV/AIDS 3

Research Toward a Cure 4

HIV-Associated Coinfections, Comorbidities, and Other Complications 5

Crosscutting Research for HIV/AIDS 6

- Basic Research 6
- Health Disparities 7
- Training 7

Foreword

I am pleased to present the FY 2017 Trans-NIH Plan for HIV-Related Research. The Office of AIDS Research (OAR) is the only entity at the National Institutes of Health (NIH) that sets trans-NIH HIV/AIDS research priorities and builds a budget based on those priorities.

In August 2015, Dr. Francis Collins, the NIH Director issued a statement identifying the overarching HIV/AIDS research priorities for the NIH for the next 3 to 5 years (http://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-nih-efforts-focus-research-end-aids-pandemic). The NIH also simultaneously issued new HIV/AIDS research priorities for determining HIV/AIDS funding (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-137.html).

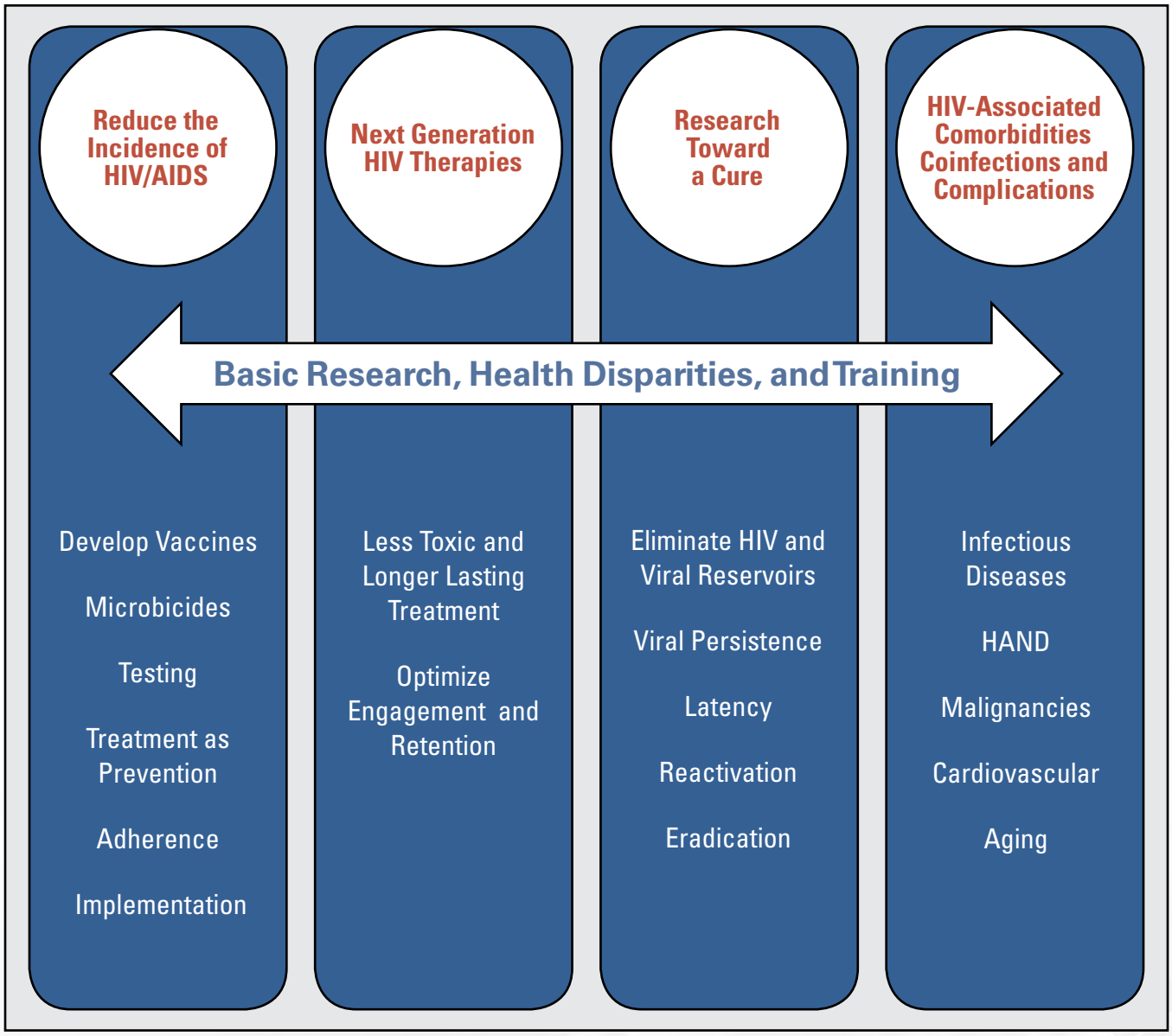
We have made extraordinary strides in HIV/AIDS research, including the development, use and implementation of biomedical and behavioral modalities for HIV/AIDS diagnosis, prevention, and treatment. There is still a great deal more to do, however, both in the United States and internationally. The need for a safe and effective vaccine, strategies for achieving a cure, and the reduction of health disparities among various vulnerable populations with respect to HIV/AIDS outcomes are critical.

We remain strongly committed to supporting important and crucial HIV/AIDS research that will have a major impact on ending the AIDS pandemic. We encourage HIV/AIDS investigators to propose innovative strategies to prevent, treat, and eventually cure AIDS. This Strategic Plan provides a blueprint for progress forward to meet those challenges so that we can someday live in a world without AIDS.

- **Legislative Mandate** Section 2353 of the Public Health Service Act requires that the Director of OAR shall: (1) establish a comprehensive Plan for the conduct and support of all AIDS activities of the agencies of the NIH; (2) ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; (3) ensure that the Plan establishes objectives regarding such activities; (4) ensure that all amounts appropriate for such activities are expended in accordance with the Plan; (5) review the Plan not less than annually, and revise the Plan as appropriate; and (6) ensure that the Plan serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of specific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan. The law also specifically requires that the Plan provides for basic research, applied research, research conducted by the NIH, research supported by the NIH, proposals developed pursuant to solicitations by the NIH and investigator-initiated proposals, and behavioral and social sciences research. In accordance with the law, the NIH Office of AIDS Research, a component of the NIH Office of the Director in the Division of Program Coordination, Planning, and Strategic Initiatives, has developed this Strategic Plan.
- **The NIH HIV/AIDS research program** is coordinated and managed by OAR, which functions as an "institute without walls" with responsibility for HIV/AIDS-related research supported by almost every NIH Institute and Center (IC). OAR coordinates the scientific, budgetary, and policy elements of this diverse trans-NIH research program. OAR plans and coordinates NIH HIV/AIDS research through development of the annual Trans-NIH Plan for HIV-Related Research that identifies the overarching research priorities. This process involves scientists from across the NIH and other federal agencies, nongovernment experts, and community constituency groups. The Plan also serves as the framework for developing the annual trans-NIH HIV/AIDS research budget to ensure that research dollars are invested in the highest priority areas of scientific opportunity that will lead to new tools ending the HIV/AIDS pandemic, developing a safe and effective AIDS vaccine, developing a cure, and achieving an AIDS-free generation. As required by law, the Director of OAR and Director of NIH together determine the total allocation of AIDS research dollars. OAR determines each IC's AIDS research allocation based on the Trans-NIH Plan for HIV-Related Research, scientific opportunities, the evolving clinical profile of the epidemic, and the IC's capacity to absorb and expend resources for the most meritorious science. It is not based on a formula. This process reduces redundancy, promotes harmonization, and ensures cross-Institute collaboration. The NIH investment in HIV/AIDS research has produced groundbreaking scientific advances, which continue to provide a critical foundation of knowledge, tools, and strategies for achieving the goals of the President's National HIV/AIDS Strategy. The NIH will continue to sponsor research in search of solutions to prevent, treat, and ultimately, cure HIV/AIDS.

With sincere appreciation,
Robert W. Eisinger, Ph.D.
NIH Acting Associate Director for AIDS Research
Acting Director, Office of AIDS Research

Overarching HIV/AIDS Research Priorities



Overarching HIV/AIDS Research Priorities for AIDS Funding

- **Reduce the incidence of HIV/AIDS, including:** developing and testing promising vaccine, microbicide and pre-exposure prophylaxis candidates and novel methods of delivery, especially those with potential to mitigate adherence issues; and developing, testing, and studying strategies and the implementation of strategies to improve HIV testing, and entry, and maintenance in prevention care and services.
- **Next generation of HIV therapies with better safety and ease of use, including:** developing and testing HIV treatments that are less toxic, longer acting, have fewer side effects and complications, and easier to take and adhere to than current regimens; implementing research to understand how best to initiate treatment as soon as an HIV diagnosis has been made, improving engagement and retention in care; and achieving and maintaining optimal prevention and treatment responses.
- **Research toward a cure, including:** developing novel approaches and strategies to identify and eliminate viral reservoirs that could lead toward a cure or lifelong remission of HIV infection, including studies of viral persistence, latency, reactivation, and eradication.
- **HIV-associated coinfections, comorbidities, and complications, including:** addressing the impact of HIV-associated comorbidities, including tuberculosis, malignancies, cardiovascular, neurological, and metabolic complications; and premature aging associated with long-term HIV disease and antiretroviral therapy.
- **Crosscutting areas:** Basic research, health disparities, and training, including:
  - **Basic Research:** understanding the basic biology of HIV transmission and pathogenesis; immune dysfunction and chronic inflammation; host microbiome and host and viral genetics that impact susceptibility to infection and disease outcomes; and other fundamental issues that underpin the development of high-priority HIV prevention, cure, comorbidities, and treatment strategies.
  - **Research to Reduce Health Disparities** in the incidence of new HIV infections or in treatment outcomes of those living with HIV/AIDS.
  - **Research Training** of the workforce required to conduct high-priority HIV/AIDS or HIV/AIDS-related research.

Reducing the Incidence of HIV/AIDS

Significant advances in treatment have had major impact on the health of millions of HIV-infected individuals. To bring an end to the HIV/AIDS pandemic, however, new infections need to be prevented. Multiple approaches will be necessary to end the pandemic. Specific areas of NIH prevention research include: active and passive vaccines; antiretroviral (ARV) and non-ARV microbicides; multipurpose prevention technologies (MPTs); voluntary medical male circumcision (VMMC); ARVs for the prevention of mother-to-child transmission; pre-exposure prophylaxis (PrEP); and treatment as prevention (TasP) to reduce the risk that an HIV-infected individual will transmit the virus to an uninfected partner. Prevention studies should include socio-behavioral strategies to reduce risk, synergize other prevention technologies, and gain and sustain prevention adherence. Appropriate animal models continue to be critical in responding to preclinical questions concerning strategies for HIV prevention, including understanding of the immune responses, viral uptake, and mechanisms of infection, and determining the safety and potential efficacy of agents prior to engaging in clinical research. Given that most HIV-infections occur at mucosal surfaces, it is essential to better understand mucosal immune functions and properties, including the role of the microbiome, which can contribute to protection from HIV infection.

Successful interventions and treatments depend on individual and community readiness, acceptance, and implementation into practice. The NIH supports behavioral and social sciences research to better understand the factors that support or prevent HIV risk, transmission, and acquisition, and influence demand for and adherence to effective prevention and treatment strategies. The NIH will continue to support a comprehensive HIV/AIDS research portfolio that includes basic and behavioral and social sciences research for those populations at highest risk of infection, developing and incorporating socio-behavioral interventions, and implementing studies to reduce the incidence of HIV/AIDS.

High-priority research opportunities focused on reducing the incidence of HIV/AIDS include:

- Examining the relationship between the genital/rectal-anal tract microenvironment, host factors, immune function, microbiome, and HIV risk, transmission, and acquisition.
- Evaluating the role of immunity (including, but not limited to T cells, B cells, antigen-presenting cells, innate responses and host factors), particularly at mucosal sites, for protection in the context of studies on vaccines, microbicides, and long-acting antiretroviral agents.
- Conducting clinical trials for vaccines, microbicides, MPTs, PrEP, and other biomedical prevention modalities.
- Developing and testing standardized assays to better understand the mechanisms of infection and transmission that inform vaccine, microbicides, and PrEP efficacy.
- Developing models to study the contributions and interactions of behavioral, social, structural, and environmental factors in at-risk communities, as well as models for community engagement to reduce HIV/AIDS in different populations and cultural settings.
- Identifying strategies to overcome barriers to the adoption, adaptation, integration, scale-up and sustainability of evidence-based interventions and tools, as well as clinical guidelines (standards of care) while accounting for racial, ethnic, cultural, gender, sex, and age differences in diverse settings.

Next Generation Therapies for HIV/AIDS

NIH-sponsored research has led to critical advances in the development and clinical testing of antiretroviral therapy (ART), which has transformed HIV into a chronic manageable disease. ART results in profound immune recovery and enhanced function in HIV-infected individuals who are able to adhere to prescribed HIV treatment regimens and tolerate the side effects and toxicities. With the expansion of the classes of antiretroviral drugs, simplified daily regimens, and an array of combination treatments, sustained viral suppression is routinely achievable. ART has not only delayed the progression of HIV disease to AIDS, but also it has been effective at maintaining viral suppression and thus innate immunity, with the accompanying benefit of delayed development of viral resistance. The NIH will continue to support a comprehensive HIV/AIDS therapeutics research portfolio that includes drug discovery, preclinical drug development, clinical testing of new drugs and multidrug therapeutic regimens with improved safety, and identification of new and novel targets to allow for durable suppression of viral activity.

High-priority research opportunities focused on next generation therapies for HIV/AIDS include:

- Elucidating the mechanisms of HIV persistence in persons on maximally suppressive ART and developing and testing strategies to promote and prevent the establishment of viral reservoirs as well as their elimination.
- Accelerating the discovery and validation of novel agents and strategies aimed at new and existing viral and cellular targets to develop safe, tolerable, low-cost, and maximally long-term suppressive antiviral activity.
- Developing and testing existing and novel agents that can be used alone or in combination with behavioral and other strategies to maximize viral suppression and adherence to antiretroviral drug regimens to prevent and treat HIV disease.

Research Toward a Cure

Combination ART has radically changed the course of HIV infection by improving health, prolonging life, and substantially reducing the risk of HIV transmission; however, it does not result in a cure. Although ART is effective in treating HIV disease, there remain toxic side effects, continued risks for HIV-associated clinical complications, and the need for lifelong therapy that are significant burdens on the HIV-infected individual, family and social structures, and the health systems that care for them. The experience of the "Berlin Patient" has demonstrated that sustained viral remission is possible. Subsequent research suggests that interventions resulting in sustained HIV remission off ART that are safe, effective, and scalable could be an achievable goal in the near term. Lifelong remission and/or viral eradication will be a more challenging and long-term goal. A major hurdle to achieving a cure is the ability of HIV to rapidly establish reservoirs of latent virus within the body through integration of viral genes into the genome of certain cell types. Additional research is needed to better understand the mechanisms and dynamics of HIV persistence and latency in reservoirs of long-lived cells, even in the presence of effective ART. Further research on models of HIV infection in non-human primates and small animals will be critical, as is the need for continued studies to advance the development of novel cure interventions.

High-priority research opportunities focused on research towards a cure include:

- Understanding viral and host mechanisms–including differential tissue and cellular distribution–that direct HIV persistence, latency, and reservoir formation.
- Developing and testing novel interventions, including therapeutic vaccines and next-generation monoclonal antibodies and derivatives, to control or eliminate latent and/or persistent reservoirs of HIV in the presence of effective ART.
- Identifying and validating novel biomarkers, assays, and imaging techniques to advance research toward a cure.

HIV-Associated Coinfections, Comorbidities, and Other Complications

HIV/AIDS is a disease in large part defined by coinfections and comorbid conditions. Frequently, HIV infection and its complications do not occur in isolation, but rather are preceded and co-occur with other health and mental health issues such as substance abuse, mental disorders, and malnutrition. With the advent and widespread use of ART, there has been a significant change in the types of HIV-associated coinfections, comorbidities, and complications that are seen, but the challenges of HIV clinical management continue globally. Examples are numerous and include, but are not limited to: tuberculosis, hepatitis B and C, and other sexually transmitted infections (STIs). Comorbidities include cardiovascular disease, metabolic abnormalities and diabetes/insulin resistance, bone and muscle disease, liver and kidney disease, neurological disorders, including cognitive decline, as well as AIDS-defining and non-AIDS defining cancers, and frailty in people aging with HIV. A unique challenge, particularly in low-resource and international settings, is the existence of multiple, preexisting, and concurrent comorbid conditions. Epidemiologic studies continue to identify new HIV-related comorbidities and help to differentiate effects related to long-term ART use from those related to HIV disease and suboptimal immune function. Development of new agents, alone and in combination, as well as novel sustained release formulations and delivery systems may impact the prevention and treatment of co-infections, comorbidities, and other long-term HIV-associated complications.

High-priority research opportunities focused on HIV-associated co-infections, comorbidities, and other complications include:

- Accelerating the discovery, testing, and validation of therapeutic strategies to prevent and treat HIV-associated comorbidities across the lifespan of HIV-infected individuals.
- Elucidating the mechanisms responsible for the pathogenesis of comorbid conditions of various organ systems, including the contribution of the immune system, inflammation, and long-term antiretroviral therapy on the development of these comorbidities.
- Defining the mechanisms that increase the risk of acquiring HIV-associated coinfections in diverse populations, and evaluating the interaction of coinfecting pathogens on HIV disease progression and vice versa.
- Examining the prevalent comorbidities such as substance use and abuse, mental disorders, and malnutrition within the context of HIV/AIDS.

Crosscutting Research for HIV/AIDS

A major proportion of HIV/AIDS research has relevance to not one, but all of the overarching NIH HIV/AIDS priority research areas. This includes basic research, health disparities research, and training.

Basic Research

Basic research provides the underlying foundation for all HIV/AIDS studies. This component of the NIH HIV/AIDS research portfolio includes research to examine HIV virology, transmission, acquisition, and host-viral interactions. Additionally, it includes critical research on the viral, cellular, and molecular mechanisms of HIV-associated clinical complications. This research is crucial to better understand the development of HIV-associated comorbidities, and the acquisition and pathogenesis of coinfections. These studies elucidate the genetic and immune mechanisms involved in HIV disease progression, as well as determine how sex, gender, age, ethnicity, culture, race, pregnancy, nutritional status, and other factors influence disease and treatment outcomes as well as susceptibility to HIV infection.

High-priority research opportunities focused on basic research include:

- Furthering the understanding of host-viral interactions, including cellular and immune responses, the role of the microbiome, host restriction, and host and viral genetics to inform the highest priority HIV/AIDS research.
- Developing and improving research models to advance research on HIV transmission, acquisition, acute and chronic infection, latency and persistence, pathogenesis, microbicides, vaccines, and treatment.
- Developing new tools, standards, biomarkers, systems biology, behavioral-social-contextual factor analytics, and other novel methodologies for the evaluation and design of biomedical and behavioral research interventions.

Health Disparities

Despite profound advances in research, there are significant health disparities with respect to HIV/AIDS treatment outcomes, particularly morbidity and mortality. These disparities can be linked to race, socioeconomic status, country of origin and gender, as well as in other marginalized, hidden, or "hard-to-reach" groups, such as refugees, migrant workers, adolescents, and rural populations. The NIH has and will continue to prioritize the enrollment and retention of individuals of diverse racial, ethnic, and cultural backgrounds, sex and gender minorities, and individuals with preexisting conditions in clinical trials. Studies have repeatedly delineated that these significant health disparities are critical drivers of the HIV/AIDS pandemic and are related to disproportionate HIV risk, acquisition, transmission, and poor treatment outcomes. Unraveling the complex interplay between these factors is essential to decrease the rates of HIV transmission and seroprevalence among these populations, but also increase–by extension–early diagnosis and access to services, treatment adherence, reducing the gap in treatment outcomes, and minimizing HIV-associated comorbidities and comortalities. Biologic, social and behavioral, and implementation research is needed to identify not only the optimum combination of interventions and strategies, but also how effective these will be in achieving the goals of reduced acquisition and transmission, while enhancing HIV treatment adherence, retention in care, and improved outcomes. Such a broad agenda of research will require identifying opportunities for individual, community, and population level interventions.

High-priority research opportunities focused on HIV-related health disparities include:

- Utilizing clinical, epidemiological, behavioral, basic, and implementation science research to enhance the understanding of the impact of race, ethnicity, culture, socioeconomic status, gender, and other social determinants of health on HIV acquisition, prevention and transmission, diagnosis, treatment, and clinical management.
- Expanding existing research methods and developing innovative methodologies to accurately assess biological, contextual, social, and individual facilitators and inhibitors of HIV transmission, infection and disease progression in racial, ethnic, cultural, gender, and sexual minority populations across the lifespan.
- Developing HIV diagnostic, prevention, and therapeutic technologies, as well as expanding implementation science to determine the impact and cost effectiveness of existing interventions and strategy combinations, improving uptake and scale-up, and providing an evidence base to inform clinical practice in diverse settings.
- Strengthening the broad dissemination of HIV/AIDS research information to inform clinical practice in diverse populations and settings, including, but not limited to, the centralization and availability of large cohort data.

Training

The NIH supports the training of a research workforce to build the critical capacity and infrastructure to conduct HIV/AIDS research globally. This includes teaching, evaluating, and maintaining the highest bioethical standards in the conduct of HIV research, as well as developing and maintaining collaborations and leadership in HIV/AIDS research and its related sciences.

High-priority research opportunities focused on training include:

- Promoting and supporting training, capacity building, and infrastructure development critical to enhancing HIV/AIDS research.

NIH
DEPARTMENT OF HEALTH & HUMAN SERVICES · USA