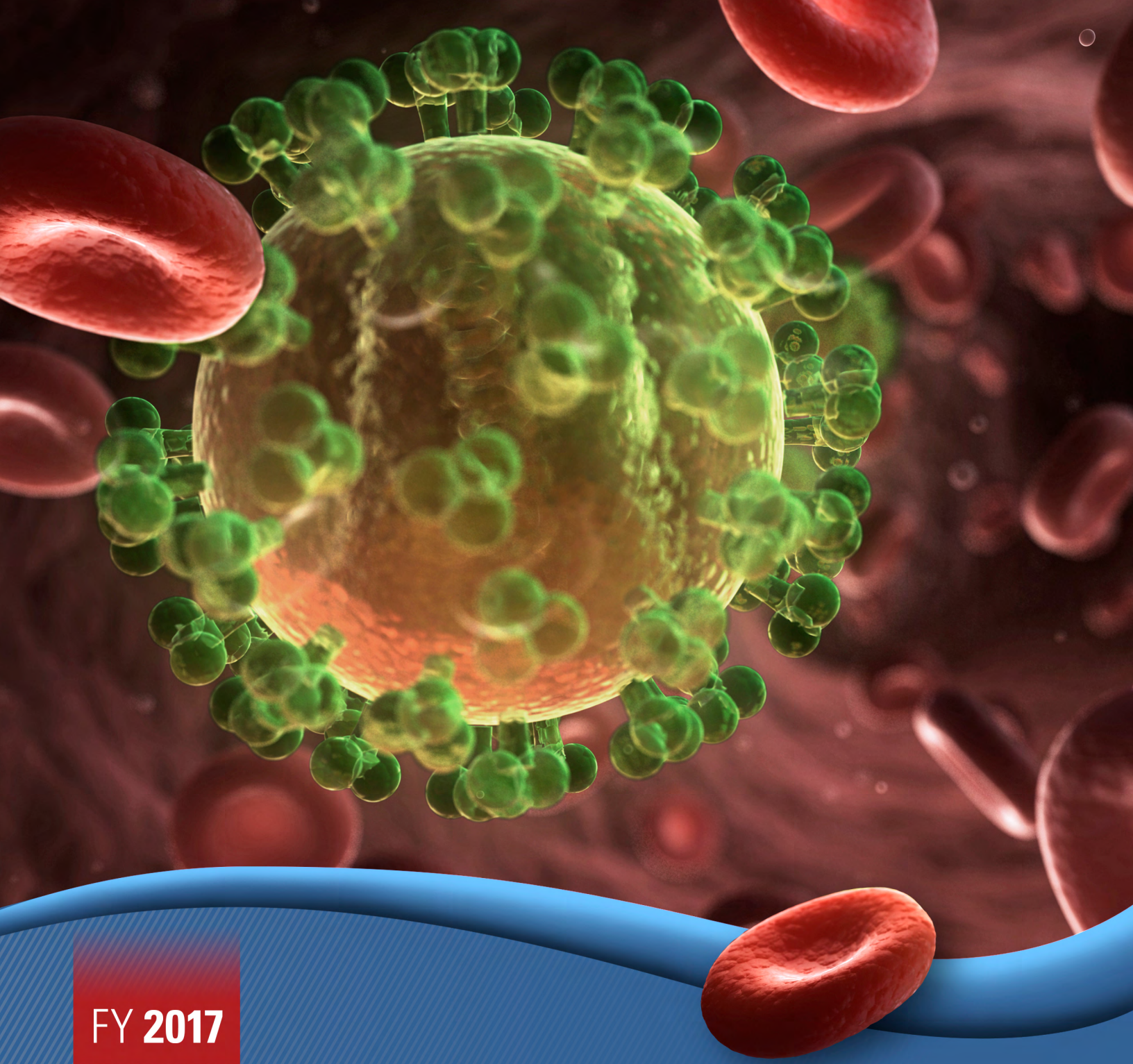


FY **2017**

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

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).

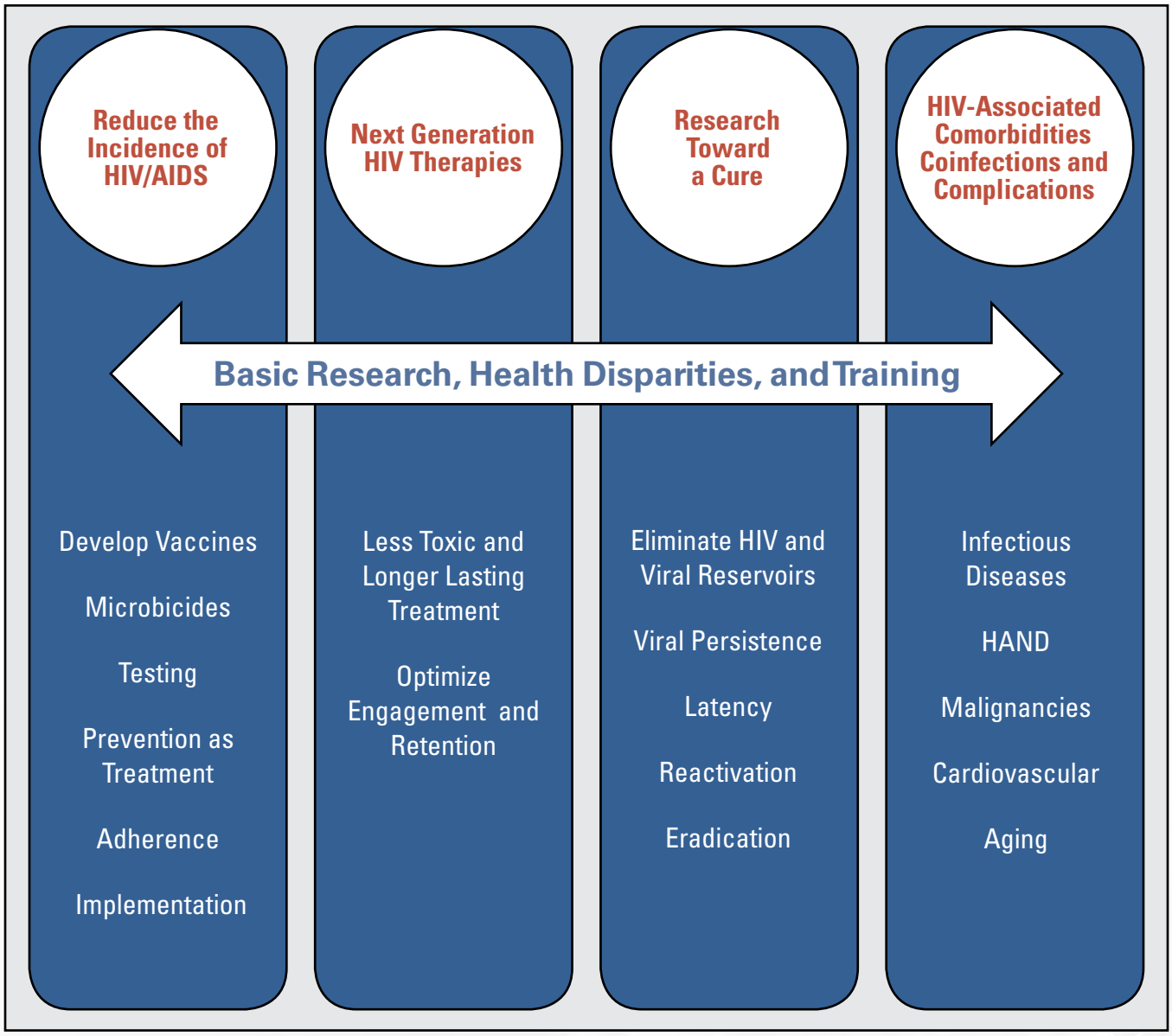
We have made extraordinary strides in HIV/AIDS research, including the development, use and implementation of biomedical and behavioral modalities for HIV/AIDS diagnosis, prevention, and treatment. There is still a great deal more to do, however, both in the United States and internationally. The need 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.