FY 2016

National Institutes of Health

TRANS-NIH PLAN FOR HIV-RELATED RESEARCH

Prepared by the Office of AIDS Research
Jack Whitescarver, Ph.D.
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Participants at the 20th International AIDS Conference (AIDS 2014) in Melbourne, Australia, pay tribute to AIDS researchers who lost their lives aboard Malaysian Airlines Flight MH17 on July 17, 2014.

Dedicated to the memory of the more than 30 million people who have died since the HIV/AIDS epidemic was first recognized, including the estimated 1.6 million lives lost this past year, and to the more than 35 million people who are living with HIV/AIDS today.

Contents

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 provide 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, has developed this Strategic Plan.

"It is by now a cliché, but nonetheless true, that research progress against HIV and AIDS clearly illustrates the fundamental unity of science."

William E. Paul, M.D.
Former 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." The Joint United Nations Programme on HIV/AIDS reports that in 2013:

- More than **35 million** people were estimated to be living with HIV/AIDS; the majority do not have access to HIV prevention, care, and treatment; and approximately half are unaware they are infected.
- Approximately **2.1 million** people became HIV-infected, or about **6,000 new infections per day.**
- **1.5 million** people died of AIDS-related illnesses. Deaths have declined due in part to scale-up of antiretroviral therapy, but HIV remains a leading cause of death worldwide and the number one cause of death in Africa.
- HIV has led to a resurgence of tuberculosis (TB), particularly in Africa, and TB is a leading cause of death for people with HIV worldwide.
- Women represented more than 50 percent of all adults living with HIV worldwide. HIV is the leading cause of death among women of reproductive age.
- Thirty-three percent of new infections were among young people, aged 15–24.
- There were **3.2 million** children living with HIV, 240,000 new infections among children, and 190,000 AIDS deaths.
- Global mother-to-child transmission rates in the absence of antiretroviral drug administration to the mother and infant were 15–30 percent, and increased to 45 percent with breastfeeding.

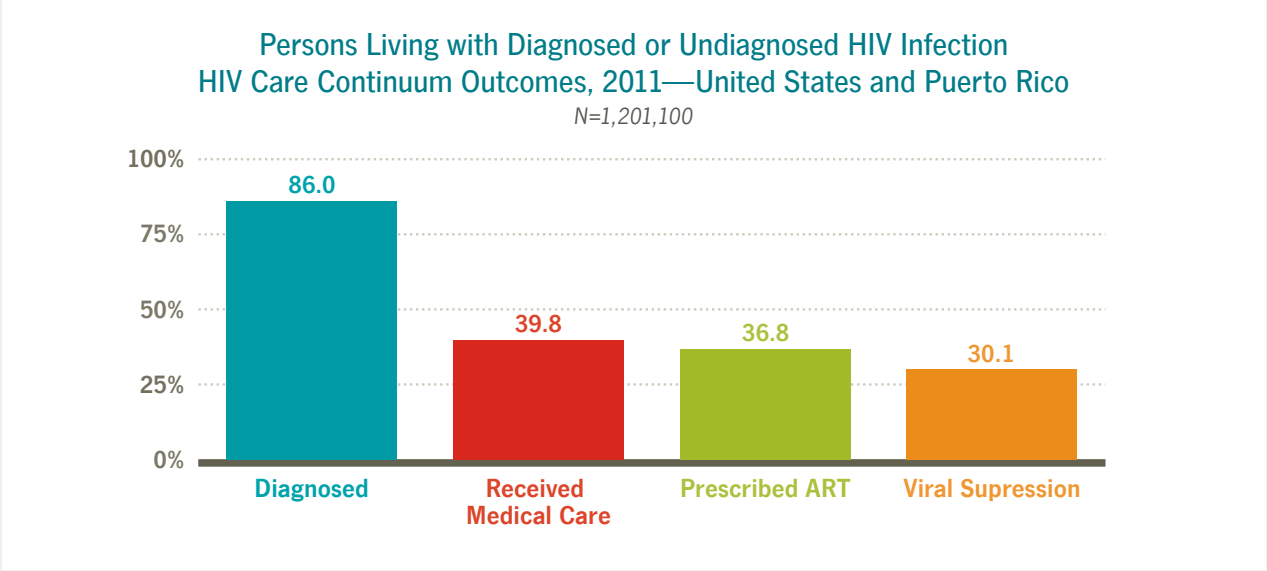
The AIDS Epidemic in the United States

The Centers for Disease Control and Prevention reports that:

- Today, more people are living with HIV than ever before, as people are living longer with HIV disease, and the number of new infections remains relatively stable.
- More than **1.2 million** people are living with HIV.
- More than **650,000** people have died.
- New infections have remained at about **50,000** per year for more than a decade.
- **Forty-five percent** of new infections occur in the South, the region where HIV-infected patients have lower survival rates and tend to be younger, more rural, African American, Hispanic, and female.
- While many people with HIV are diagnosed (86 percent), far fewer are engaged in care (40 percent) and are prescribed antiretroviral therapy (37 percent).
- **Only 30 percent of HIV-infected individuals 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 share that is even lower among blacks (28 percent) and young people aged 25–34 (23 percent).

SOURCE: National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention

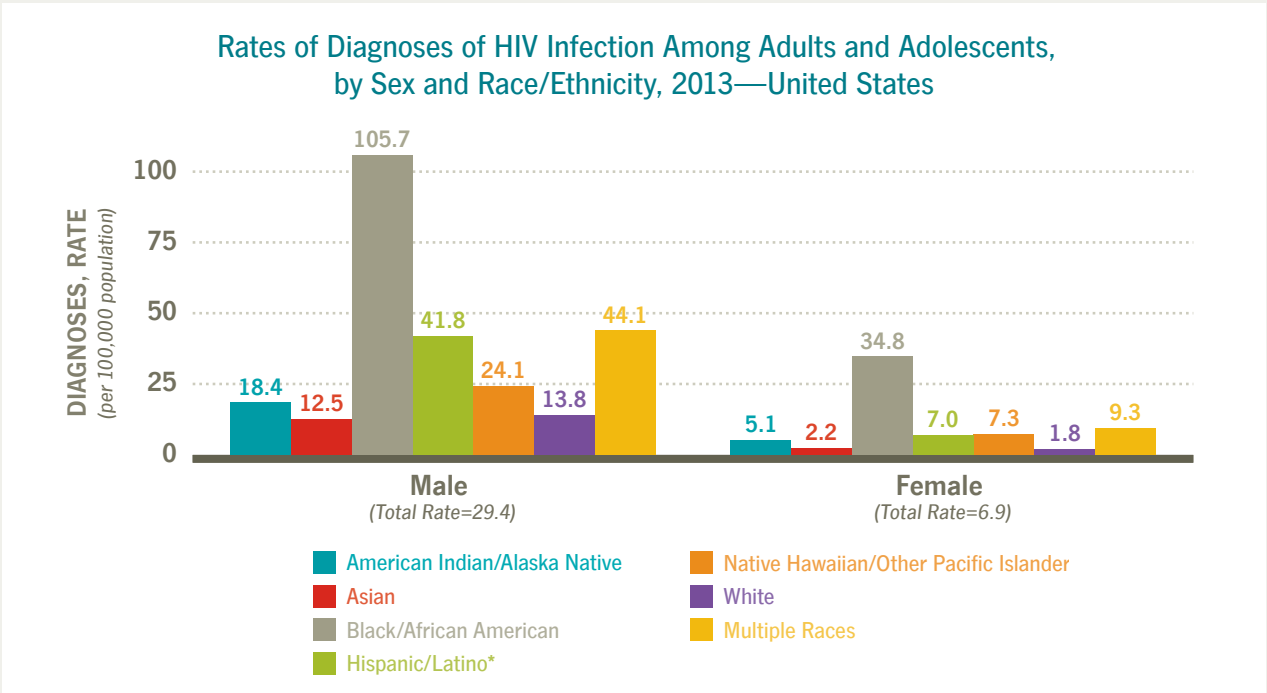
HIV Care Continuum in the United States



National HIV Surveillance System: Estimated number of persons aged ≥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 aged ≥18 years who received HIV medical care during January to April of the specified year, were prescribed antiretroviral therapy (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

Foreword by the Director of the Office of AIDS Research

I am pleased to present the *FY 2016 Trans-NIH Plan for HIV-Related Research*. The Office of AIDS Research is the only entity at the National Institutes of Health (NIH) that sets trans-NIH research priorities and builds a budget based on those priorities.

AIDS is not over. We have made critical and even breathtaking progress in AIDS research against many odds. We have been challenged to confront and address stigma, homophobia, racial disparities, and criticisms of the AIDS research investment. We have come a long way, but the AIDS pandemic is far from over and remains a threat to global populations. Any declaration that the end is near is premature, inaccurate, and perilous to progress against the pandemic.

AIDS research has been one of the NIH's best investments; now is not a time to throttle down or step back from that investment. We cannot dissipate our dedicated workforce of brilliant AIDS scientists nor discourage the next generation of young investigators from joining the fight to conquer AIDS. The NIH must continue to search for critical solutions to prevent, treat, and eventually cure AIDS.

This Strategic Plan provides a blueprint for progress forward to meet those challenges so that we can some day live in a world without AIDS.

Jack Whitescarver, Ph.D.
NIH Associate Director for AIDS Research and
Director, Office of AIDS Research

Research Accomplishments and Challenges

National Institutes of Health (NIH)-sponsored research has brought about remarkable scientific advances. Among the more recent accomplishments are:

- Development of new treatments for many HIV-associated coinfections, comorbidities, malignancies, and clinical manifestations;
- Development of new strategies for the prevention of mother-to-child transmission, which have resulted in dramatic decreases in perinatal HIV in the United States, where fewer than 100 babies a year are born with HIV infection;
- Demonstration of the first proof of concept that a vaccine can prevent HIV infection, and identification of potential immune markers for protection;
- Discovery of more than 20 potent human antibodies that can stop up to 95 percent of known global HIV strains from infecting human cells in the laboratory;
- Demonstration that the use of antiretroviral therapy (ART) by infected individuals can dramatically reduce HIV transmission to an uninfected partner;
- Demonstration of the effectiveness of pre-exposure prophylaxis, the use of ART regimens by uninfected individuals to reduce their risk of HIV acquisition;
- Discovery that genetic variants may play a role in enabling some individuals, known as "elite controllers," to control HIV infection without therapy;
- Critical basic science discoveries that continue to provide the foundation for novel research;
- Identification of potent human neutralizing antibodies that successfully suppressed a nonhuman form of HIV in primates, which may lead to new treatment strategies and novel research to potentially cure HIV;
- Production and analysis of proteins that may provide an important new pathway in AIDS vaccine design; and
- Advances in basic and treatment research aimed at eliminating viral reservoirs in the body that are leading scientists to design and conduct promising and novel research aimed at a cure for HIV/AIDS.

The NIH is leading global research efforts to capitalize on all these advances, move science forward, and turn the tide against this pandemic. Although the science of AIDS has never been more promising, it is critical to point out that:

- Although AIDS is a treatable disease, the drugs have side effects and toxicities that complicate management of the disease; even with treatment, many HIV-infected individuals experience early signs of aging and comorbidities, such as cardiovascular disease and neurologic deterioration.
- Neuropsychological impairment was detected in approximately 52 percent of HIV-infected individuals in the United States receiving ART.
- Critical challenges remain to develop a vaccine, optimize treatment toward a cure, and prevent and treat the many serious comorbidities and complications, such as AIDS-related malignancies, that compromise increasing numbers of patients.
- More than half of the total NIH AIDS research budget is devoted to basic science that provides the crucial basis for HIV prevention and treatment research and provides information that benefits other areas of research beyond AIDS.
- The advances in AIDS research continue to provide benefit to research on many other diseases, including cancer, Alzheimer's disease, and other infectious diseases.
- The AIDS pandemic will remain the most serious global public health crisis of our time until better, more effective, and affordable prevention and treatment regimens—and eventually a vaccine and a cure—are developed and available around the world.
- *The end of AIDS remains far in the future; it is too soon to declare victory, and it is critical to sustain the research effort.*

Image courtesy of Shutterstock, Inc.; used by permission.

The Office of AIDS Research (OAR) and the Trans-NIH AIDS Research Program

- OAR's mission is to establish a unified NIH research agenda to address the AIDS pandemic.
- This research program encompasses all NIH Institutes and Centers (ICs) and is a comprehensive program of basic, clinical, behavioral, and translational research on HIV infection, its associated coinfections, opportunistic infections (OIs), malignancies, and other complications.
- This program includes unprecedented trans-NIH scientific coordination and management of research funds.
- A trans-NIH strategic planning process is conducted annually to identify the highest scientific priorities and opportunities to address the evolving epidemic.
- The annual trans-NIH budget is based on the Strategic Plan.
- Trans-NIH coordination, management, and evaluation are conducted.
- Domestic and international collaborative AIDS research agreements are facilitated and implemented.

The NIH AIDS research program is coordinated and managed by OAR, which functions as an "institute without walls," with responsibility for AIDS-related research supported by every NIH IC. Because AIDS affects virtually every organ system, and results in a myriad of HIV-associated infections, malignancies, comorbidities, and clinical complications, NIH AIDS research supports a vast portfolio that also includes these related illnesses and conditions, such as tuberculosis, hepatitis, and AIDS-associated cancers, neurologic complications, and cardiovascular conditions. OAR coordinates the scientific, budgetary, and policy elements of this diverse trans-NIH research program that encompasses the efforts of nearly every NIH IC—a complex, comprehensive, multidisciplinary, and global research response to the pandemic.

Annual Trans-NIH Strategic Plan

OAR plans and coordinates this research through the development of an annual trans-NIH Plan that identifies overarching AIDS-research priorities and specific research objectives. The Plan serves several important purposes:

- It is the framework for developing the trans-NIH AIDS research budget.
- It determines the use of NIH AIDS-designated funds and tracks and monitors those expenditures. The Plan thus defines those research areas for which AIDS-designated funds may be allowed.
- It is a document that provides information to the public, the scientific community, Congress, and the AIDS-affected communities about the NIH AIDS research agenda.
- OAR distributes the annual comprehensive Plan to a wide audience, and it appears on the OAR Web site: *http://www.oar.nih.gov/strategicplan/*.

This comprehensive and unique annual process involves scientists from across the NIH and other Government agencies, nongovernment experts, and constituency groups. During the planning process, the state of the science is reviewed, newly emerged and critical public health needs are assessed, and scientific opportunities are identified. The annual process culminates with the identification of the highest strategic priorities and critical research needs.

Within the NIH, OAR established coordinating committees, consisting of NIH staff members, to develop the Plan for each specific area of HIV/AIDS research. The members of the coordinating committees represent those NIH ICs with the most significant research portfolios in the scientific areas. The coordinating committees developed the first draft of the Plan. The charge to the committee members was to update the Plan, addressing the process strictly from the perspective of the priorities of overall scientific areas, and not from an IC-specific perspective. Outside planning groups for each area, comprising experts from academia, foundations, AIDS organizations, and community representatives, also contributed to each section of the Plan. The draft Plan also was sent to each IC director and IC AIDS coordinator for their recommendations and suggested additions or changes.

A list of all the planning process participants can be found in Appendix A.

Priority-Setting Review

The OAR Advisory Council (OARAC) also has reaffirmed the key scientific priorities. OARAC conducted a priority-setting portfolio review of the entire AIDS research program to reexamine and affirm the highest priorities for NIH AIDS research. These priorities also address the goals of the President's National HIV/AIDS Strategy and the President's Executive Order concerning the HIV Care Continuum. OAR will continue to allocate and redirect resources across the ICs and across the key areas of science to address these priorities and the changing clinical profile of the pandemic.

The report of this review can be found in Appendix B.

International AIDS Society/Steve Forrest

International AIDS Society President Dr. Chris Beyrer; Nobel Laureate Dr. Françoise Barré Sinoussi; Ambassador Eric Goosby; and OAR Director Dr. Jack Whitescarver

Annual Trans-NIH AIDS Research Budget

OAR is mandated to develop an annual trans-NIH AIDS research budget in partnership with the ICs and explicitly tied to the objectives of the Strategic Plan. The law provides that OAR "shall receive directly from the President and Director of the OMB all funds available for AIDS activities of the NIH" for allocation to the ICs in accordance with the Plan.

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

The careful determination of the balance of the research budget—among ICs, across areas of science, between intramural and extramural research programs, between basic and clinical research, and between investigator-initiated and targeted research—requires a comprehensive knowledge of the science and of the ICs' portfolios. Funds are allocated to the ICs based on the priorities of the Plan, scientific opportunities, and the ICs' capacity to absorb and expend resources for the most meritorious science—not on a formula. This process reduces redundancy, promotes harmonization, and ensures cross-IC collaboration. At the time of the appropriation, OAR informs each IC of its AIDS-related budget allocation, specifying amounts for each approved initiative. OAR also has a 3 percent transfer authority to move funds across ICs during the fiscal year.

Because OAR is authorized to manage AIDS resources as an "institute without walls," the total for NIH AIDS research includes both extramural and intramural research across the NIH ICs (including research management support, a management fund, and a service and supply fund), buildings and facilities, and training and evaluation for research on HIV/AIDS and its many associated comorbidities and complications. The total for AIDS-related research is therefore not comparable to spending reported by the NIH for individual diseases in the Research, Condition, and Disease Categorization (RCDC) system, which reflects primarily extramural investments.

Key Research Priorities for FY 2016

The key scientific priorities that shape this Plan are:

- **Prevention Research:** Research to prevent transmission and acquisition of HIV infection, including basic research on HIV, that will underpin further development of critically needed vaccines, microbicides, and other biomedical prevention strategies, including the use of ART as prevention.
- **Research Toward a Cure:** Research related to the potential for a cure or lifelong remission of HIV infection, including studies on viral persistence, latency, reactivation, and eradication.
- **Optimization of Therapeutics:** Research to develop and assess therapies that are more effective in suppressing viral replication; less toxic; longer acting; have fewer side effects and complications, such as premature aging comorbidities; and more likely to achieve eradication of infection. This includes research to address unique characteristics, such as gender, race/ethnicity, age, nutritional status, genetics, and history of violence and trauma that may influence treatment success or failure.
- **Coinfections, Comorbidities, and Complications:** Research on the treatment and prevention of HIV-related coinfections, malignancies, and neurological, cardiovascular, and metabolic complications.
- **Basic Research:** Research focused on the transmission, acquisition, establishment, and maintenance of HIV infection, and on the cause of its associated profound immune deficiency and severe clinical complications.

The Importance of AIDS Research to Other Research Areas

It is important to point out that the NIH investment in AIDS research has resulted in critical scientific accomplishments that not only have benefited the 35 million HIV-infected individuals around the world, but also have contributed knowledge to the prevention, diagnosis, and treatment of many other diseases and conditions. AIDS research deepens our understanding of immunology, virology, microbiology, molecular biology, and genetics.

AIDS research is helping to unravel the mysteries surrounding so many 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 unleashes a myriad of OIs, comorbidities, cancers, and other complications). For example:

- AIDS immunology and biology research also has informed the understanding of inflammation.
- 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 cognitive manifestations ultimately will benefit millions of patients with Alzheimer's disease and other aging and dementia issues.
- 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.
- 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 AIDS-associated OIs also now benefit patients undergoing cancer chemotherapy and the more than 28,000 Americans who receive organ transplants each year.
- AIDS research has advanced understanding of the relationship between viruses and cancer. New research has demonstrated that a drug used to treat HIV may slow prostate cancer.

New investments in AIDS research will continue to fuel biomedical advances and breakthroughs that will have profound benefits far beyond the AIDS pandemic.

Structure of the Strategic Plan

The Plan is structured to comprehensively describe the biomedical and behavioral research and training activities that are needed to address the AIDS pandemic, define specific research priorities, and reflect mutual reinforcement among the scientific and crosscutting areas. Since the development of the first Strategic Plan in 1993, the Plan has been divided into a series of Scientific Areas of Emphasis. *All AIDS-designated funds are coded by the ICs and tracked by OAR by the objectives of these areas.*

SCIENTIFIC AREAS OF EMPHASIS

PREVENTION RESEARCH

- Vaccines
- HIV Microbicides

OPTIMIZATION OF THERAPEUTICS

- Drug Discovery, Development, and Treatment
- Antiretrovirals as Prevention

CROSSCUTTING AREAS

- Etiology and Pathogenesis
- Natural History and Epidemiology
- Behavioral and Social Science
- Training, Infrastructure, and Capacity Building
- Information Dissemination

Over the years, OAR has adapted the structure of the Plan to address new scientific opportunities and the shifting demographics of the pandemic. Areas of Special Interest have been added. *Funding for these areas is coded and tracked in the aggregate, but not by objective, as the dollars are captured within the scientific areas.* (Note: Research Toward a Cure will become a Scientific Area of Emphasis in the FY 2017 budget).

AREAS OF SPECIAL INTEREST

- Research Toward a Cure
- Women and Girls
- Racial and Ethnic Populations
- Research in International Settings

For all of these areas, the Plan provides:

- **PRIORITIES:** The priorities detailed in each section represent current areas requiring focused attention, gaps in current knowledge, or areas of special scientific opportunity.
- **OBJECTIVES:** The objectives present overarching areas of inquiry to address the priorities.

SCIENTIFIC AREAS OF EMPHASIS

Prevention Research

Vaccines

The best long-term hope for controlling the AIDS pandemic is the development of safe, effective, and affordable AIDS vaccines that can be used in combination with other prevention strategies. The National Institutes of Health (NIH) supports a broad AIDS vaccine research portfolio encompassing basic, preclinical, and clinical research, including studies to identify and better understand potentially protective immune responses in HIV-infected individuals and studies of improved animal models for the preclinical evaluation of vaccine candidates. Information gained from these studies is being used to inform the design and development of novel vaccine strategies.

Since the modest success of the RV144 trial in Thailand using a pox virus vector and HIV envelope protein boosts, the NIH has supported unprecedented international collaborative investigations to identify how specific immune responses may protect against HIV acquisition. Samples from the HVTN 505 trial in the United States with DNA and adenovirus vectors are being subjected to similar analyses to understand why that vaccine strategy failed to protect against HIV acquisition. To build on the knowledge gained from these studies, clinical trials in other populations and in other parts of the world with new and potentially improved products and alternative vectors have been designed and are currently underway. Recent data from several Phase I and Phase II vaccine clinical studies present new scientific opportunities for the development of improved HIV vaccine candidates.

FY 2016 RESEARCH PRIORITIES

- **Explore new HIV vaccine approaches to engage T-cell help for germinal center B cells, in particular, long-lived plasma cells producing protective antibodies. This includes studies to understand the nature and quality of innate immunity to HIV immunogens induced by adjuvants and vectors and the process of inducing unique CD8 or CD4 T cells. Inform vaccine design by incorporating systems biology approaches and large dataset analyses from these and other preclinical and clinical studies to pinpoint where immune responses can be modulated to improve protective immunity.** HIV vaccine research continues the quest to determine why broadly neutralizing antibodies to HIV envelope are so difficult to elicit, given multiple constructs and strategies tested. When anti-envelope responses are detected in uninfected vaccine recipients, they are usually weak, of very limited breadth, and not durable. Approaches for co-administration of vector and improved protein immunogens, as well as those evaluating proteins or selected epitopes with novel adjuvants to provide sustained antigen exposure, may offer insights into how to initiate appropriate early innate signals and T-cell help, leading to optimal B-cell responses.

- **Design and conduct *in vivo* experiments to test the potential functions of non-neutralizing antibodies, particularly in the control of infection at mucosal barriers, in the control of cell-to-cell spread of infection, or in the control of viral replication and dissemination from the initial site of infection.** Many antibodies have been identified from HIV-infected individuals that have extended breadth across clades with the potential to neutralize HIV *in vitro* and prevent infection in animal models. Additional antibodies possessing an array of potential *in vitro* activities resulting in control of viral replication have been identified from vaccine recipients. Studies suggest that these latter antibodies can synergize with broadly neutralizing antibodies and may lead to prevention and control of HIV/simian immunodeficiency virus (SIV). Underpinning these experiments is a need for full characterization of the rhesus macaque genome, in particular genes for immunoglobulins and Fc receptors in existing and emerging animal models.

- **Continue to invest in novel approaches for designing better HIV immunogens to increase the breadth of T-cell as well as B-cell immune responses.** Multiple approaches to improved immunogen design have been developed and tested to overcome limited responses to highly glycosylated HIV envelope proteins. Additional innovative concepts need to be evaluated in preclinical studies and small experimental trials in humans to determine why some constructs that appear to be improved antigens fail to generate broad immune responses. Expanded studies to understand the requirements for immunogenicity and the pathways for broader recognition of conserved neutralizing epitopes are warranted.

- **Plan and conduct HIV vaccine efficacy studies in the emerging environment of overlapping prevention methods in the United States and in international populations at high risk for HIV infection.** As we move forward with HIV vaccine studies, it is essential that planning incorporate the option for enrollees to choose one or more recently demonstrated HIV prevention interventions, such as voluntary medical male circumcision and use of antiretroviral (ARV) drugs. Although these interventions may not be uniformly implemented by individual volunteers in HIV vaccine studies, the combined effect of vaccine with other prevention methods will be required to interpret the efficacy of future trials.

- **Develop mentorship opportunities for new investigators in the HIV vaccine field, enabling them to translate promising preclinical vaccine studies in nonhuman primates into human clinical trials.** There are limited opportunities for new investigators in the field of HIV vaccines to be mentored in translational science, knowledge of which is required to successfully bridge preclinical and clinical studies. This has been raised repeatedly as a significant barrier for attracting and retaining new investigators to pursue careers in HIV vaccine research, and in infectious disease research in general. This comes at a time when new tools and methodologies in the analysis of genetics and large datasets are increasingly being used to understand the complexity of immune responses to HIV and other vaccines to human pathogens. These emerging challenges will require a new cadre of investigators trained across several disciplines.

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Adaptive and Innate Host Defense Mechanisms. Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

OBJECTIVE–B: Vaccine Design, Development, and Animal Testing. Design HIV antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other U.S. Government agencies, nongovernmental organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations such as breastfeeding infants, adolescents, and women.

OBJECTIVE–C: Active and Passive Pediatric Vaccines. Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

OBJECTIVE–D: Conduct Phase I, Phase II, and Phase III Vaccine Clinical Trials. Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate HIV vaccines or concepts in domestic and international settings.

OBJECTIVE–E: Research and Preparation for HIV Vaccine Clinical Trials. Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of HIV vaccine trials, while balancing the prevention needs of the at-risk populations, including women and adolescents; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize the feasibility of vaccine studies in appropriate cohorts or populations.

HIV Microbicides

A safe and effective microbicide will be an important asset to the HIV prevention toolkit. Microbicides are products, including ARV drugs and other agents, which could be applied topically or injected to prevent acquisition of HIV and other sexually transmitted infections (STIs). Microbicides could be used alone or in combination with other strategies.

The NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, formulation, preclinical testing, and clinical evaluation of microbicide candidates. The NIH supports basic science research aimed at understanding how HIV crosses mucosal membranes and infects cells. In addition, the NIH supports behavioral and social science research on adherence to, and the acceptability and use of, microbicides among different populations. These projects include the safety of microbicide use during pregnancy and menopause, studies in adolescents and in men who have sex with men, and implementation research to better understand how to integrate a potential product into community prevention practices.

Basic science and clinical studies have shown promise for the use of ARV-based microbicides as HIV prevention strategies. Studies are underway and being developed to test different ARV- and non-ARV-based products; the safety of various microbicide formulations, including long-acting formulations; the safety and pharmacokinetics of microbicides combined with a contraceptive for multipurpose prevention; and microbicides combined with antimicrobial agents to simultaneously prevent HIV and other STIs. Microbicide formulations and new technologies that enhance adherence—such as injectable products, nanofibers and particles, ARV-containing films, and intravaginal rings—also are being developed and studied. The NIH will continue to support the discovery, design, development, formulation, and evaluation of microbicide candidates and the maintenance of a robust pipeline that includes both ARV and non-ARV products.

FY 2016 RESEARCH PRIORITIES

- **Develop, maintain, and advance a sustainable and diverse pipeline of ARV- and non-ARV-based microbicide candidates and multipurpose prevention technologies (MPTs) with varied formulations for use in men and women across the lifespan that prevent HIV, HIV and other STIs, and/or HIV and pregnancy.** A diverse and robust microbicide product pipeline is needed to ensure the availability of prevention products that are acceptable for use in men and women at varied times in the lifespan and under varied circumstances. A variety of topical application formulations that may or may not be coitally dependent could broaden the acceptability of microbicides to varied populations and subgroups under different sexual circumstances. ARV-based and non-ARV-based microbicide products will be needed to address concerns about using microbicides composed of ARVs that are currently used for treatment and the risk for ARV resistance. MPTs may be an effective approach to reducing stigma associated with microbicide product use.

- **Develop and standardize models and biomarkers of safety, efficacy, adherence, HIV exposure, and sexual activity for microbicide and MPT studies.** Standard animal and cell models for safety and efficacy, and biomarkers for adherence, HIV exposure, and sexual activity, will facilitate the interpretation of data from microbicide and MPT effectiveness studies and inform the development and maintenance of a robust microbicide product pipeline. The development of standards for pharmacokinetic (PK) and pharmacodynamic (PD) correlates, including tissue PK and PD of product efficacy, also will inform the interpretation of data on safety, adherence, and efficacy from all phases of microbicide research studies.

- **Determine the changes that occur in the genital tract and anal/rectal mucosa, including the mucosal microenvironment, that may affect HIV acquisition and transmission in men and women across the lifespan.** There is increasing data that support the importance of understanding how the genital and anal/rectal immune function and microenvironment, including the microbiome, influence HIV acquisition and risk across the lifespan. Information

is needed to better understand how anatomic and cellular changes, endogenous and exogenous hormones, STIs and bacterial vaginosis, vaginal and anal/rectal practices such as douching and the use of lubricants, and sex and sexual trauma may affect biologic HIV risk across the lifespan. Particular attention is needed to understand how these intersecting factors influence HIV risk and acquisition in adolescent females and males—the populations most at risk for HIV infection.

- **Develop, test, and standardize models for community engagement in microbicides research to better understand product desirability, create products that meet individual and community needs, and support product implementation.** Community engagement in the conceptualization of microbicide products, including product formulations, may facilitate the development of more acceptable candidate microbicides and greater adherence. Understanding the social and behavioral community constructs that govern HIV risk and the use of prevention methods could assist in the development and testing of candidate microbicides that demonstrate greater effectiveness. Understanding community and social norms that lead to stigma associated with the use of HIV prevention interventions could inform the development of candidate microbicides and the design of microbicide studies.

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Basic Mechanisms of Mucosal Transmission. Elucidate basic mechanisms of HIV transmission and protection for virus and host factors at mucosal surfaces important for the development of microbicides and MPTs.

OBJECTIVE–B: Discovery, Development, and Preclinical Testing. Support the discovery, development, and preclinical evaluation of ARV- and non-ARV-based microbicide and MPT candidates.

OBJECTIVE–C: Formulations and Modes of Delivery To Optimize HIV Prevention. Develop and evaluate safe, acceptable, and effective formulations and modes of delivery, including long-acting agents for ARV- and non-ARV-based microbicides and MPTs.

OBJECTIVE–D: Conduct Microbicide and MPT Clinical Trials. Conduct clinical safety and efficacy studies on candidate microbicides and MPTs that include assessments of acceptability and adherence.

OBJECTIVE–E: Conduct Microbicide Behavioral and Social Science Research. Conduct basic and applied behavioral and social science research to inform and optimize the desirability and effectiveness of candidate microbicides and MPTs.

OBJECTIVE–F: Microbicides Infrastructure. Establish and maintain the infrastructure needed to conduct research on microbicides and MPTs.

SCIENTIFIC AREAS OF EMPHASIS

Optimization of Treatment

Bruce Forster/Getty Images

OPTIMIZATION OF TREATMENT

Drug Discovery, Development, and Treatment: NIH-sponsored research has been a critical component of the therapeutic advances achieved in HIV treatment, with a number of successes ranging from the identification of the first targets for drug development to the drug combinations and regimens used for treatment of HIV infection. Building on the identification of the critical therapeutic interventions that have allowed for the interruption of mother-to-child transmission, the NIH continues to probe areas of critical importance for successful treatment of HIV infection and managing the inflammatory, metabolic, cardiovascular, and renal complications that often ensue. A comprehensive AIDS therapeutics research portfolio must include drug discovery, preclinical development and clinical testing of new drugs, and multidrug therapeutic regimens, as well as identification of new and novel targets to allow for suppression of antiviral activity. It is essential that this research focus on individuals in both resource-limited and resource-intensive settings and across their lifespan.

Antiretroviral therapy (ART) has resulted in profound immune recovery and enhanced function in patients who are able to adhere to prescribed HIV treatment regimens and tolerate the side effects and toxicities associated with antiretroviral drugs. With the expansion of the classes of ART available, the regimens required to provide viral suppression have been greatly simplified. ART not only has delayed the progression of HIV disease to AIDS, but also it has been increasingly effective at prolonged viral suppression and delayed development of viral resistance. The addition of integrase inhibitors to the ART arsenal has enhanced treatment options for the treatment experienced, and novel options for greater virologic control for the treatment naive. Unfortunately, the challenge continues to be the ongoing morbidity and mortality associated with the complications of long-term HIV infection, including, but not limited to, tuberculosis (TB), hepatitis B and C, metabolic dysregulation due to HIV infection and its treatment, as well as AIDS- and non-AIDS-defining cancers.

Antiretrovirals as Prevention: A critical area of prevention research is the study of treatment strategies as a method to prevent new HIV infections. This approach builds on NIH-sponsored landmark clinical trials that demonstrated the treatment of HIV-infected pregnant women could significantly reduce transmission of HIV from mother to child. Recent groundbreaking studies have demonstrated the successful use of antiretrovirals to prevent transmission of HIV in specific populations. Clinical results

from a large NIH-sponsored international clinical trial (HIV Prevention Trials Network [HPTN] 052) showed that early initiation of antiretroviral treatment of HIV-infected heterosexual individuals resulted in a 96 percent reduction in sexual transmission of HIV to their uninfected partner. Another major NIH-sponsored clinical trial—the Chemoprophylaxis for HIV Prevention in Men study, also known as iPrEx—demonstrated that daily use of an antiretroviral drug by some high-risk, uninfected men could reduce their risk of acquiring HIV. The findings from this study showed proof of concept and the effectiveness of a novel HIV prevention strategy known as pre-exposure prophylaxis (PrEP). Recent studies have shown PrEP to be effective in preventing HIV acquisition among two at-risk populations: women in heterosexual discordant couples and injection drug users; these findings are helping to lay the groundwork for clinical guidance for the widespread use of PrEP. The NIH supports ongoing basic, translational, clinical, and implementation research to develop combinations of antiretroviral drugs and compounds that can be used in sustained release formulations for potential new PrEP strategies; test PrEP in high-risk uninfected populations, including adolescents; evaluate post-exposure prophylaxis, which is the use of ART to prevent infection after HIV exposure, including in a health care setting; develop improved regimens to prevent mother-to-child transmission; and evaluate a potential innovative prevention strategy known as "test and treat" to determine the impact of increased testing with immediate referral to treatment at the community level.

FY 2016 RESEARCH PRIORITIES

- Accelerate the discovery and validation of strategies targeting new and existing viral and cellular targets that might provide safe, tolerable, and maximally long-term suppressive antiviral activity.
- Accelerate the discovery and validation of therapeutic strategies to prevent progression of HIV and to treat its associated comorbidities, including, but not limited to, coinfections; inflammation; cancer; as well as the cardiovascular, hepatic, metabolic, neurologic, renal, and other clinical complications across the lifespan of HIV-infected individuals.
- Support research to interrupt mother-to-child transmission of HIV infection, including effective strategies to prevent transmission through breastfeeding, as well as interventions to prevent acute infection (horizontal transmission) in pregnant and breastfeeding women.
- Develop, test, and evaluate methods, tools, and intervention strategies designed to improve entry and retention in HIV care and treatment.
- Develop and test strategies to improve adherence to antiretroviral drug regimens and regimens designed to prevent and treat HIV-associated comorbidities.

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Discover and Develop Anti-HIV Treatments. Identify and validate viral and host cellular functions required for HIV replication that can be targeted for inhibition, eradication of persistent virus, and prevention of transmission. Discover and develop novel agents and therapeutic strategies, with special emphasis on those that have novel targets, effective against drug-sensitive and drug-resistant virus, and, if possible, sustained release formulations to allow less frequent dosing. Encourage collaborations between academia, industry, private and public organizations, the community, and the NIH.

OBJECTIVE–B: Conduct Clinical Research of HIV Treatments in Treatment Naive and Treatment Experienced Individuals. Through the conduct of clinical trials and cohort studies (including clinical pharmacology studies) determine the short- and long-term efficacy, effectiveness, and safety of novel strategies and therapeutic agents against acute, established, or latent HIV infection, and viral reservoirs. Develop and evaluate new clinical trial methodologies and strategies for identifying and eliminating tissue reservoirs of HIV. Develop and evaluate strategies (including cost-effectiveness studies) to improve care, care linkage, retention and antiviral adherence, as well as mitigate the many factors that adversely affect the success of therapeutic strategies. Assess strategies to more effectively monitor antiretroviral adherence in treated individuals other than self-report, including objective biomarkers of exposure. There are many factors demonstrated to interfere with treatment adherence, including mental illness, substance and alcohol use, stigma, cognitive impairment, as well as acculturative and domestic trauma and their sequelae. All of these factors contribute to poor treatment adherence

and thus poorer treatment outcomes for those affected by these conditions. Develop strategies for diagnosis and treatment of the sequelae of sexual trauma and intimate partner violence among persons with HIV. Develop domestic and international partnerships to design and conduct clinical studies in high-prevalence locations.

OBJECTIVE–C: Approaches to Managing the Consequences of HIV Infection and Its Treatment. Develop strategies to predict, prevent, treat, and evaluate the complications of long-term HIV disease and the toxicities of ART (including but not limited to cardiovascular, renal, and metabolic disorders); investigate the role of inflammation in the pathogenesis of these complications and comorbidities found in HIV infection.

OBJECTIVE–D: Prevent and Treat HIV-Associated Coinfecting Agents and Coinfection. Develop and evaluate new agents and strategies for diagnosis, prevention, and treatment of the most significant infections related to HIV, including, but not limited to, TB, malaria, hepatitis C virus (HCV), hepatitis B virus (HBV), and Kaposi's sarcoma-associated herpesvirus (KSHV). Develop and evaluate new therapeutic agents and strategies to prevent and treat drug-resistant coinfections, particularly TB.

OBJECTIVE–E: Approaches to Interrupt Vertical Transmission and Preserve Maternal Health. Develop and assess strategies to prevent mother-to-child HIV transmission (MTCT), with emphasis on strategies to prevent transmission through breastfeeding, as well as the short- and long-term effects of interventions for preventing MTCT on the health of HIV-infected women and HIV-exposed, uninfected infants and children.

OBJECTIVE–F: Strategies for Preventing Horizontal Transmission. Evaluate the impact of ART and immunotherapeutic agents in HIV-infected and -uninfected patients, and their roles in the prevention of horizontal HIV transmission in at-risk populations, such as adolescents, drug users, men who have sex with men, discordant couples attempting conception, pregnant and breastfeeding women, and transgender individuals.

OBJECTIVE–G: Treatment of HIV-Related Neurologic and Neuropsychiatric Disorders. Develop strategies to assess, prevent, and treat HIV nervous system infection, as well as the neurologic and neuropsychiatric complications of HIV disease (including treatment-associated toxicities).

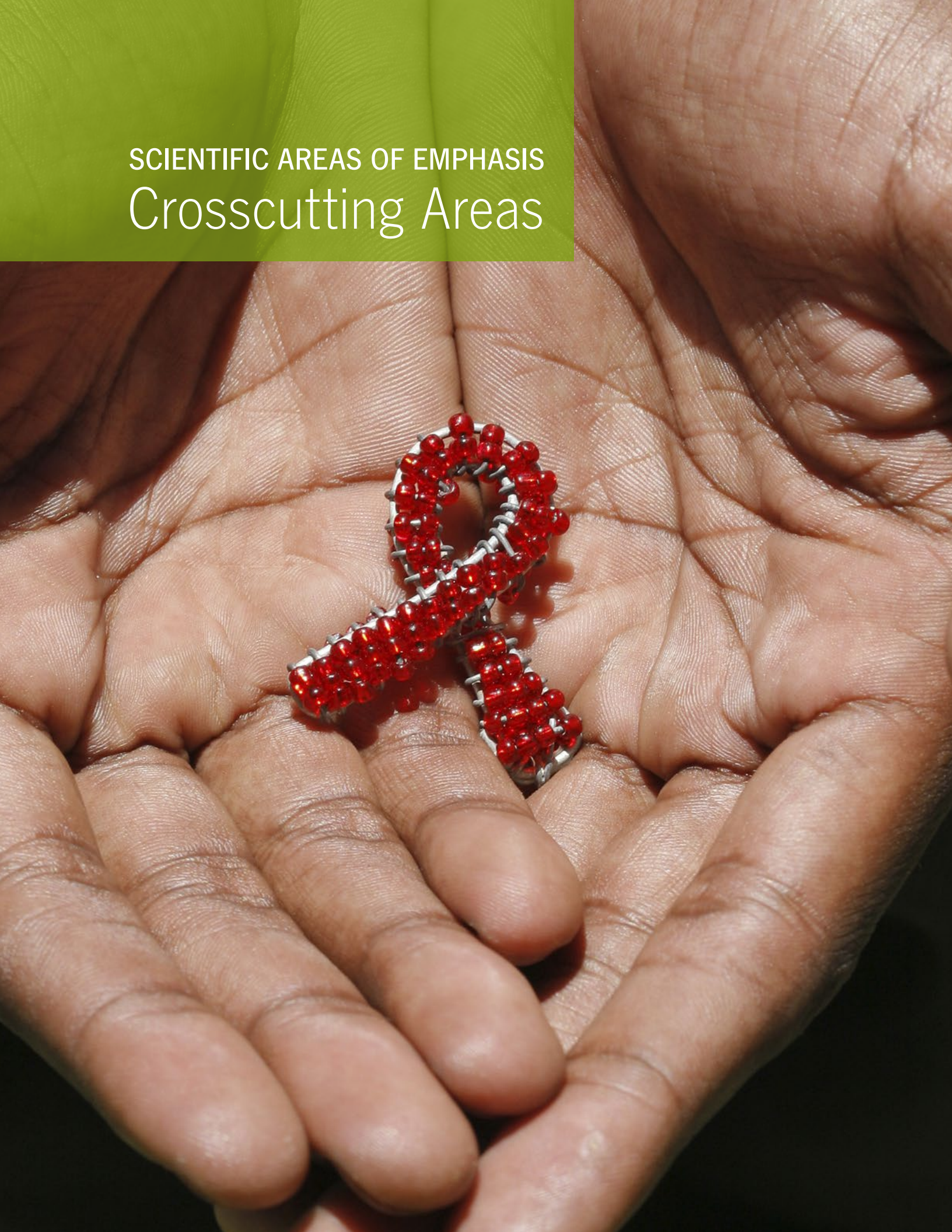
OBJECTIVE–H: Assessment, Prevention, and Treatment of HIV-Associated Cancers and Cancers in HIV-Infected Individuals. Develop and evaluate improved strategies for the assessment, treatment, and prevention of cancer as a comorbidity of HIV disease.

OBJECTIVE–I: Immune Reconstitution Therapeutic Approaches. Develop and assess therapeutic approaches that will restore, sustain, and enhance the immune system in HIV-infected individuals.

OBJECTIVE–J: Nonpharmacologic and Complementary Approaches to HIV Infection and Its Management. Develop and assess novel interventions (e.g., nonpharmacologic complementary and alternative medicine) for the prevention and symptom management of HIV disease and its complications.

SCIENTIFIC AREAS OF EMPHASIS

Crosscutting Areas



Etiology and Pathogenesis

The National Institutes of Health (NIH) supports a comprehensive portfolio of research focused on the transmission, acquisition, establishment, and maintenance of HIV infection and the causes of its associated profound immune deficiency and severe clinical complications. Research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, methodologies for diagnosis of HIV infection, and tools for monitoring disease progression and the safety and effectiveness of antiviral therapies.

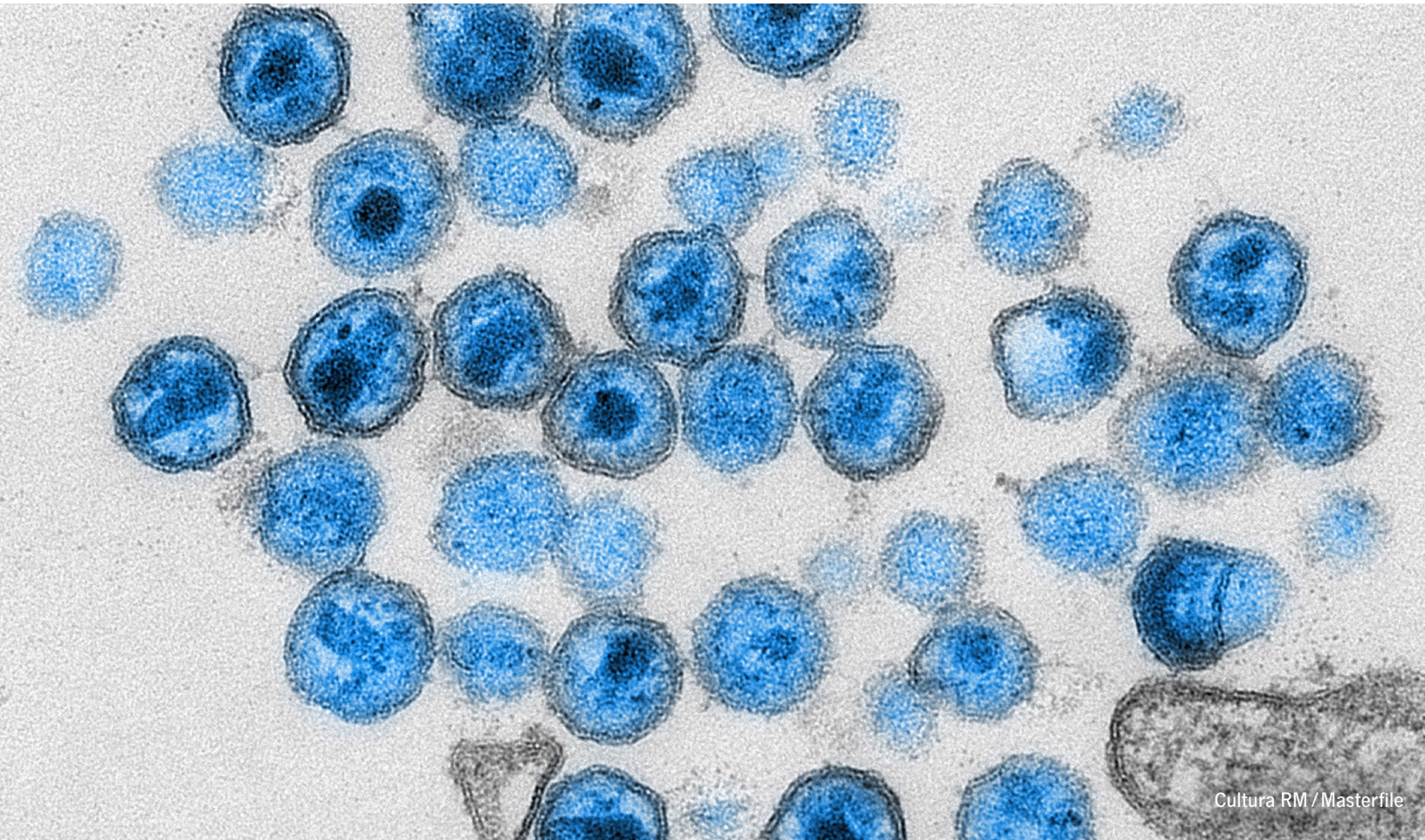
Groundbreaking strides have been made toward understanding the fundamental steps in the life cycle of HIV, the host–virus interactions, and the clinical manifestations associated with HIV infection and AIDS. Additional research is needed to further the understanding of the virus and how it causes disease, including studies to delineate how sex, gender, age, ethnicity, race, pregnancy, nutritional status, and other factors interact to influence vulnerability to infection and disease progression; to determine the role of immune dysfunction and chronic inflammation in HIV pathogenesis; and to further the understanding of the development of HIV-associated comorbidities, such as cardiovascular, neurological, and other clinical complications, malignancies, and coinfections (including tuberculosis [TB] and hepatitis C). Research examining the host microbiome as well as the genetic determinants associated with HIV susceptibility, disease progression, and treatment response also is needed.

These studies may lead to the development of customized therapeutic and preventive regimens formulated for an individual patient based on his or her genetic sequence. The NIH also prioritizes research examining the mechanisms by which HIV establishes and reactivates latent reservoirs of infection and studies that further the understanding of factors that are associated with the ability of the host to restrict HIV infection and/or mitigate HIV disease progression. A better understanding of these processes could help identify key targets for the development of new therapeutic and vaccine strategies to prevent or control HIV infection and possibly lead to a cure for HIV disease.

FY 2016 RESEARCH PRIORITIES

- Further the understanding of viral mechanisms and host factors associated with the acquisition, transmission, replication, control, tolerance, and persistence of HIV at the molecular, cellular, tissue, organ, and organism levels. Elucidate the mechanisms of pathogenesis, including determinants of disease progression versus non-progression, innate immune factors, pattern of infected cells, and the mechanisms and role of the immune activation response and inflammation cell-targeting and immune homeostasis.
- Understand the pathogenesis of the residual disease occurring in antiretroviral therapy (ART)-treated HIV-infected individuals. This includes, from the virological point of view, the role of persistent virus replication and the presence of reservoirs of latently infected cells, and from the immunological point of view, the role of residual immune activation and inflammation, the incomplete CD4+ T-cell reconstitution, and premature immune senescence.
- Understand the role of innate immunity, including specific cell types, soluble factors, and cellular effectors, in acquisition, primary infection, disease progression, and immunopathogenesis, as well as understand how they collectively influence the establishment of the founder virus, severity of the primary infection, long-term outcome of disease, and triggering of the acquired immune response.
- Study the effect of the CD4+ T-cell pool heterogeneity in terms of differentiation (naive, stem-cell memory, central memory, transitional memory, and effector memory), lineage (Th1, Th2, Th17, Treg, Tfh), anatomic location (blood versus lymphoid tissues versus mucosal tissues), and expression of markers of activation/exhaustion.

- Identify the cell types, tissue types, and body sites where the HIV reservoirs reside and determine the mechanisms of persistence. Improve assays to measure the size of the reservoir and develop strategies to contain, eradicate, and induce cytopathic killing and the immunoclearance of HIV reservoirs.
- Study the interaction of aging with HIV infection and the mechanisms responsible for the pathogenesis of comorbid conditions associated with aging to include research on the relative contribution of the immune system, immune response to infection, inflammation, and long-term ART on these comorbidities.
- Elucidate the pathogenesis and sequelae of HIV-related coinfections, the perturbations of comorbidities, non-AIDS-defining cancers, and the pathogen–pathogen and pathogen–host synergistic interactions that define mechanisms in HIV-infected individuals that contribute to the development and progression of these conditions.
- Study the role of the microbiome and its interaction with the host in HIV acquisition, transmission, replication, pathogenesis, comorbidities, and therapy.
- Develop new tools, standards, and methods for systems biological approaches and the analysis of big data to inform our understanding of the basic mechanisms of HIV infection within the host.
- Develop and validate novel biomarkers, as well as assays, rapid tests, and point-of-care devices, to quickly detect viral reactivation from latency and latently infected cells to assess HIV and other HIV/AIDS-related pathogen persistence in reservoirs.
- Further develop and optimize the use of relevant animal models for HIV, simian immunodeficiency virus (SIV), and chimeric simian/human immunodeficiency virus (SHIV) infection to gain further insight into the mechanisms of virus–host interaction, virus transmission, viral pathogenesis, persistence, and comorbidities; and to test novel and potentially risky interventions to better prevent and/or treat the infection in humans.



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FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Biology of HIV Acquisition and Transmission. Delineate the viral, host-genetic, epigenetic, and immune mechanisms involved in the acquisition, transmission, establishment, and dissemination of HIV in diverse populations across the spectrum of age, gender, and transmission mechanisms in domestic and international settings.

OBJECTIVE–B: HIV Virology, Viral Pathogenesis, and Viral Persistence. Delineate the viral and host mechanisms associated with HIV replication, dissemination latency, persistence, reactivation of replication-competent virus from latency, and those that influence viral setpoint, disease progression, and viral persistence in diverse populations across the spectrum of age and gender in domestic and international settings.

OBJECTIVE–C: HIV Immunopathogenesis. Delineate immunological mechanisms of HIV control, and elucidate the viral, host, and environmental mechanisms associated with HIV-induced immunopathogenesis, including immune dysfunction, aberrant immune activation, immune cell homeostasis, and inflammation across the spectrum of age, gender, and geographical location.

OBJECTIVE–D: Pathogenesis of Opportunistic Infections and Coinfections. Elucidate the pathogenic mechanisms and consequences of coinfections and their synergistic interactions with HIV, as well as the contribution of coinfecting pathogen–host interactions on disease exacerbation. Delineate the impact of significant coinfections in the context of HIV infection in diverse populations across the spectrum of age and gender in domestic and international settings and the factors that regulate susceptibility to infection or disease that might be targeted for prevention. Priority should be given to opportunistic infections (OIs) and coinfections that (a) are a major cause of morbidity and/or HIV disease progression in HIV-infected individuals and/or (b) contribute significantly to HIV acquisition or transmission.

OBJECTIVE–E: Pathogenesis of Metabolic and Body Composition Change. Define the etiology, pathophysiology, and consequences of HIV infection and treatment-related disorders; body composition changes; nutritional status; endocrine dysfunction; oral health; liver and gastrointestinal disorders; skin, muscle, and bone disorders; pulmonary disorders; nephropathy; liver disease; and cardiovascular disease in diverse populations across the spectrum of age and gender in domestic and international settings.

OBJECTIVE–F: Pathogenesis of Malignancies. Elucidate the etiologic factors, cofactors, pathogenesis, and consequences of AIDS-defining and non-AIDS-defining cancers in diverse populations across the spectrum of age and gender in domestic and international settings.

OBJECTIVE–G: Pathogenesis of Neurological Disease. Elucidate the mechanisms and consequences of HIV-associated neurological disease and neurobehavioral dysfunction in diverse populations across the spectrum of age and gender in domestic and international settings.

Natural History and Epidemiology

Natural history and epidemiologic research on HIV/AIDS is critical to the monitoring of epidemic trends, evaluation of prevention modalities, characterization of the clinical manifestations of HIV disease, and measurement of the effects of treatment regimens at the population level. Novel methodologies in the area of biostatistics, mathematical modeling, and laboratory technology have provided the basis for new epidemiological approaches in addressing HIV/AIDS. Multi-site epidemiologic studies in the United States are identifying new HIV-related comorbidities and helping to differentiate effects related to long-term ART from those related to HIV disease and chronic comorbidities. As the AIDS epidemic continues to evolve, there is a crucial need for carefully designed epidemiologic studies in domestic and international settings.

The NIH supports a comprehensive research portfolio in both settings to study the epidemiologic characteristics of populations in which HIV is transmitted and the changing spectrum of HIV-related disease, including the occurrence of coinfections (e.g., TB); malignancies; and metabolic, cardiovascular, neurological, skeletal, and other complications. These studies have delineated the significant health disparities that are critical factors in the epidemic (e.g., racial and ethnic disparities in the United States; disparities between industrialized and resource-constrained nations; disparities between men and women; and health disparities based on sexual identity). Ongoing observational studies are focusing on at-risk individuals from the U.S. rural South as well as on individuals over the age of 50. Research on HIV-related health disparities and their impact on treatment access and effectiveness, as well as on HIV prevention, will continue to be an NIH AIDS research priority.

FY 2016
RESEARCH
PRIORITIES

- **Conduct epidemiologic studies of the HIV/AIDS prevention, treatment, and care continuum at the population level through the use of individual, dyadic, community, and population-based approaches.** This priority includes the development and maintenance of HIV cohorts, with a greater emphasis on leveraging the infrastructure, databases, and specimen repositories of the large NIH-funded HIV cohorts by nonaffiliated and early-stage investigators. This priority also includes demographic-based approaches, multilevel observational studies, use and analysis of electronic health records (EHRs), and community randomized study designs. Increased attention should be devoted to the choice of the comparator population in these studies in order to accurately quantify differences between study populations and control populations, because those differences are the basis for more targeted interventions in the prevention, treatment, and care continuum. Increased emphasis also will be needed to validate and quantitate in epidemiologic studies various measures of exposure and adherence to interventions, including biological and pharmacological measures.

- **Conduct studies of HIV/AIDS and related comorbidities that provide the evidence base for the targeted implementation of research findings in diverse populations and health care circumstances.** This priority includes advancing the methodologies of implementation science and conducting implementation science studies that identify approaches to maximize the effectiveness of health programs by addressing organizational and system-level barriers at multiple levels. Specific barriers that require rigorous implementation science studies include hurdles to access to, uptake of, retention in, and scale-up and sustainability of effective HIV prevention, care, and treatment interventions. This priority also includes assessment of the applicability of particular interventions to diverse settings and among underrepresented and hard-to-reach populations, and studies evaluating the cost-effectiveness of such interventions in those settings and populations.

- **Develop novel epidemiological methods and perform the next generation of transdisciplinary HIV research.** This priority includes methods to examine the prevention, testing, and treatment cascade by integration of data from EHRs, observational studies, clinical trials, studies based on simulation and mathematical modeling, and molecular epidemiology. The breadth of epidemiological investigation on HIV/AIDS will increase through the linkage of classic and molecular epidemiology studies that use phylodynamic, phylogeographic, and pharmaco-epidemiologic analyses of representative biological samples. New method development will include interdisciplinary studies that use next-generation sequencing, transcriptomics, and metabolomics, as well as pharmacology, for analysis of large datasets in the coming era of strategic use of antivirals in prevention and treatment. It also will include broader use of informatics and information technology instruments, social networking applications, and real-time collection of information. Methodological developments in these areas will require studies validating these new technologies and their degree of robustness in diverse HIV populations and evaluating strengths and limitations of these technologies for HIV research.

- **Conduct studies that assess epidemiologic aspects of HIV infection and HIV-related disease across populations, from infancy through older adulthood.** This priority emphasizes the need to study the epidemiology of the HIV prevention, treatment, and care continuum over the life course of people affected by HIV. Both in the United States and, increasingly, in low- and middle-income countries, more widespread access to HIV treatment and care is anticipated. The proportion of HIV-infected individuals who are living with HIV to older ages is also increasing. Population-based studies will need to address the long-term effects of HIV disease, the drivers of HIV-related disparities, common coinfections, and noncommunicable disease (NCD) comorbidities in populations who are aging with HIV. Epidemiologic studies will be needed to determine which integrative syndromes (e.g., frailty in older individuals) are affected by an emerging constellation of HIV-associated risk factors (e.g., mental health, substance abuse, chronic inflammation/immune dysfunction, and polypharmacy). These epidemiologic studies, by establishing the prevalence and quantifying the burden of disease for various HIV NCD comorbidities in diverse regions and settings, will provide the knowledge base for designing screening and intervention programs across the lifespan.

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Transmission of HIV (Prevention, Risk Factors, and Mechanisms). Further characterize the relative importance of major risk factors, population-attributable risk, and mechanisms of HIV susceptibility and transmission in domestic and international settings to guide prevention and treatment strategies.

OBJECTIVE–B: Disease Progression (Including Opportunistic Infections and Malignancies). Use epidemiological research, including research through the use of EHRs, in domestic and international settings to identify the effectiveness, impact, and interactions of HIV-related therapeutics, biological factors, and behaviors; and community-level factors (e.g., HIV testing coverage) in relation to HIV progression, response to ART, and development of AIDS-defining and non-AIDS-defining chronic conditions, as indicated by virologic, immunologic, and clinical outcomes.

OBJECTIVE–C: Methodologies. Develop and evaluate methods and resources for HIV/AIDS epidemiological and clinical studies that use culturally appropriate approaches; incorporate new laboratory and statistical methods; better utilize information systems by complementing existing data; and better integrate research findings into clinical practice and regional, national, and international policies and guidelines.

Behavioral and Social Science

As studies continue to define a role for the use of ARV medications for HIV prevention, the NIH is supporting research to understand how these drugs can best be used for prevention in specific populations and social contexts. The NIH will continue to study ways to change those behaviors and social contexts and to facilitate engagement and retention in HIV testing, prevention, and treatment services. The NIH is supporting research to address factors associated with the HIV care continuum, and specifically on HIV care outcomes. Investigations are focused not only on individual-level variables, but also on social and structural issues, such as the role of stigma, housing, employment, health care access, and interpersonal networks.

Studies have suggested that modifying these variables can promote early access to medical care, reduce costs, extend life expectancy, and improve quality of life. The NIH will continue to develop new research methods. These include approaches to increase recruitment into clinical trials; to enhance statistical analyses of behaviors, such as alcohol use, that can affect medication studies; to utilize means to optimize ongoing research in light of emerging results; and to identify behavioral issues relevant to genetic or genomic studies. The NIH also will continue to foster the integration of biomedical and behavioral strategies in clinical investigations.

FY 2016
RESEARCH
PRIORITIES

- Improve the understanding of complex biological–behavioral, developmental, and social–environmental interactions that affect HIV transmission risks over the course of exposure, acute infection, chronic infection, and treatment; promote the development and use of research methods needed to capture and analyze these complex interactions, using community-based participatory research where appropriate.
- Conduct translational research (i.e., dissemination, implementation, or operational research) to foster and optimize the use of existing efficacious biomedical, behavioral, and social interventions to prevent, diagnose, and treat HIV infections and to promote access, acceptability, adherence, and continuation along the cascade from prevention to treatment, particularly among those currently underrepresented in such research (e.g., noninjection substance users, men who have sex with men [MSM], and incarcerated individuals). Behavioral and social science can contribute to more effective utilization of scientific findings by determining factors that cause adoption and continued utilization of scientific findings.
- Study the continued disparities in HIV infection rates, access to testing and care, and treatment adherence and outcomes that are manifest along racial, ethnic, and socioeconomic lines in the United States and in international settings to identify epidemiologic, sociocultural, geographical, psychosocial, and structural factors that could explain the disparities, and suggest opportunities for novel and targeted interventions to reduce them.
- Foster integration of biomedical and behavioral methods and perspectives to develop and test interventions at structural, environmental, and community levels to reduce transmission and acquisition of HIV, especially focusing on: early intervention methods addressing structural factors that have promise for large, long-term impact; the role of stigma in prevention strategies for specific communities, such as racial and ethnic populations, MSM, youth, women, transgender individuals, and young adults in high-prevalence or high-risk areas; and older adult populations engaging in risk behaviors.
- Evaluate the use of social media, mobile devices, and other rapidly changing platforms for communication, social networking, community building, and partnering as tools to reduce HIV acquisition and transmission through sexual behavior, drug use, and alcohol use, and to improve treatment adherence, recognizing the interdependencies among existing barriers and the need to address multiple levels of interventions.

- Promote the use of laboratory-based behavioral and social methods with human participants to more intensively examine risk behaviors and HIV-related outcomes to elucidate antecedents and determinants of risk, to clarify behavioral topography, to rigorously examine the role of alcohol and other drugs in risk behaviors, and to understand social forces affecting risk; develop methods to improve the ecological validity of laboratory studies.
- Evaluate approaches to maintaining the highest ethical standards in the conduct of HIV prevention science in order to ensure meaningful informed consent processes, decrease misunderstandings of the implications of clinical trial participation, minimize risk of inadvertent harm to participants, and promote justice in research through the inclusion of difficult-to-recruit but critical populations.

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Preventive Intervention Research. Conduct research to develop, evaluate, and implement behavioral, social, structural, environmental, and economic interventions that prevent HIV transmission and acquisition by targeting at multiple levels factors known or thought to drive the epidemic.

OBJECTIVE–B: Basic Behavioral and Social Science Research. Conduct basic social and behavioral research to strengthen understanding of the determinants, processes, and cultural and contextual issues influencing HIV-related risk and protective behaviors and the consequences and impact of HIV disease, including treatment for and management of HIV infection. This includes domestic and international research that examines the societal, community, organizational, social network, dyadic, and individual barriers to and facilitators of the adoption and utilization of effective preventive and treatment interventions across the life course.

OBJECTIVE–C: Consequences of HIV Infection. Conduct treatment, health, and social services research for people infected with and affected by HIV: Study the development, evaluation, diffusion, and adoption of strategies to increase early identification of HIV infection; to improve treatment adherence; and to prevent or minimize the negative physical, psychological, cognitive, and social consequences of HIV infection, including stigmatization of persons with or at risk for HIV infection. Foster research strategies for promoting effective health care utilization among all persons with HIV infection and for promoting modifications in the health care delivery system to develop more effective, socially appropriate, and culturally sensitive methods to better serve the needs of infected populations, both domestically and internationally.

OBJECTIVE–D: Research Methods. Improve the quality of behavioral and social science methodology in HIV research: Conduct research to advance innovative quantitative and qualitative methodologies to enhance the effects of behavioral and social science on HIV prevention and care, and to address pressing ethical issues in carrying out AIDS research.

Training, Infrastructure, and Capacity Building

The NIH supports the training of domestic and international biomedical and behavioral HIV researchers. The NIH also provides infrastructure and capacity-building support as integral aspects of its commitment to carrying out scientifically and ethically sound and highly productive HIV-related research. The expansion of NIH-funded HIV research globally has necessitated the development of research training and infrastructure and capacity-building efforts in many resource-limited settings throughout the world. NIH-funded programs have increased the number of training positions for HIV-related researchers, including domestic and international programs specifically designed to recruit individuals from populations underrepresented in research into research careers and to build research capacity at minority-serving institutions in the United States. Equipment, shared instrumentation, and tissue and specimen repositories are examples of the research infrastructure and capacity-building support that the NIH provides to strengthen the conduct of AIDS-related research, both domestically and internationally.

FY 2016 RESEARCH PRIORITIES

- Further develop HIV/AIDS-related training programs to promote and implement interdisciplinary research.
- Increase training for young scientists, in particular in experimental design that involves animal and other disease models of AIDS.
- Improve and further develop HIV disease animal models, including nonhuman primates.
- Support capacity building and training, both nationally and internationally, to develop new tools and collect, manage, and analyze large quantities of data from multiple sources and different formats to answer questions in HIV care, HIV comorbidities, and HIV-related genetics and genomics.
- Attract and retain HIV/AIDS scientists from around the world to conduct biomedical, clinical, and behavioral research as well as to increase the number of new investigators from diverse backgrounds.
- Promote and support the development and implementation of mentoring programs and networks to support research career development for both U.S. and international scientists.
- Promote and support infrastructure development necessary for research training with a commitment to diversity and mentoring.

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Research Training. Provide training in biomedical and social and behavioral research, including implementation science research, to address the challenges of HIV and its associated complications, coinfections, and comorbidities. Training should emphasize a multidisciplinary approach that targets research utilizing disease models as well as other tools applied to diverse populations with respect to age, gender, race, and culture.

OBJECTIVE-B: Infrastructure and Capacity Building. Develop and maintain the appropriate infrastructure and capacity needed to conduct HIV/AIDS research in both domestic and international settings.

Information Dissemination

The NIH supports initiatives to enhance dissemination of research findings, develop and distribute state-of-the-art treatment and prevention guidelines, and enhance recruitment and retention of participants in clinical studies. Effective information dissemination approaches are an integral component of HIV prevention and treatment efforts, particularly for issues related to adherence to prescribed treatments and prevention strategies, and the need to translate behavioral and social prevention approaches into practice.

The changing pandemic and the increasing number of new infections in specific population groups in the United States underscore the need to disseminate HIV research findings and other related information to communities at risk, such as racial and ethnic populations, women, older individuals, and MSM. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to use new and emerging technologies to speed the translation of research results into practice and to shape future research directions.

FY 2016 RESEARCH PRIORITIES

- **Treatment and Prevention Guidelines.** The development and distribution of state-of-the-art Federal treatment and prevention guidelines are a high priority. These guidelines are living documents that reflect the current state of knowledge for the use of new and complex ARV regimens, and the Guideline Panels continually review new data as it becomes available, incorporating changes into the documents as appropriate. The electronic versions of the guidelines on the AIDS*info* Web site (*http://aidsinfo.nih.gov/guidelines*) are the most up-to-date available and are distributed as widely as possible. AIDS*info* also creates mobile applications for popular AIDS*info* features, including an HIV/AIDS Glossary app and a Drug Database app. These apps allow access to federally approved HIV/AIDS treatment and research information optimized for mobile devices and are offered free of charge. (*http://aidsinfo.nih.gov/mobile-resources*)

- **Electronic Information Resources.** Computerized databases and other types of electronic resources are a vital component of NIH AIDS information dissemination, allowing global access to information concerning basic research, clinical trials availability and results, standards of care, and other information of interest to HIV-infected individuals, their care providers, and their advocates. The NIH offers a variety of online AIDS research information resources. *(See Appendix C.)*

- **Recruitment of Volunteers in Clinical Research.** As the number and complexity of clinical studies increase, resources must be invested in clinical trials-related information dissemination to ensure recruitment of an adequate number of participants, particularly from populations at risk, including women and racial and ethnic populations in the United States. (*http://aidsinfo.nih.gov/clinical-trials*)

- **Dissemination of Research Results/Communications/Media.** The NIH disseminates the results of important medical discoveries resulting from NIH-conducted and -supported research to improve health and save lives. The NIH utilizes multiple media platforms, including TV, radio, Web, portable communication devices, print, and social media, to reach both scientific and lay audiences. (*http://www.nih.gov/icd/od/ocpl/*)

- **Meetings, Conferences, and Workshops: Developing and Maintaining Research Collaborations and Leadership in Science.** The NIH sponsors and supports a myriad of meetings, conferences, and workshops each year that bring together scientific experts to discuss critical scientific issues and develop recommendations, research agendas, or guidelines. The participation of scientists at professional meetings is essential to the vitality of scientific endeavors—and to U.S. supremacy in biomedical research. The success of all scientific research in academia, industry, and Government depends on the formal and informal information exchanges and interactions that take place at professional conferences. These meetings represent a critical element in how science progresses.

- **Community Outreach Programs.** Providing accurate and up-to-date HIV/AIDS prevention and treatment information to communities at risk, including women and minorities, is a critical challenge. The NIH should continue to support projects to address HIV/AIDS in these populations.

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Disseminate Information to All Constituencies. Support the effective dissemination, communication, and utilization of information about HIV infection, AIDS, coinfections, OIs, malignancies, and clinical complications to all constituent communities of the NIH, domestically and internationally.

OBJECTIVE-B: Develop New Communication Strategies. Support research to identify existing gaps in communication approaches, identify and evaluate existing strategies, and develop and test new and innovative communication strategies that will improve access to and use of state-of-the-art HIV information by all relevant target audiences, domestically and internationally.

OBJECTIVE-C: Coordination and Collaboration Efforts. Develop, implement, and evaluate methods of coordination and collaboration on HIV/AIDS communication activities across NIH Institutes and Centers, among other Federal and non-Federal groups, and with international partners.

Areas of Special Interest

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Research Toward a Cure

Please note: Research toward a cure has become a priority for AIDS research over the past several years, and OAR has launched a special initiative for FY 2015–2017 to increase this area of research. In the FY 2017 Plan, Research Toward a Cure will become a separate Scientific Area of Emphasis, with separate budget coding.

Research related to the potential for a cure or lifelong remission of HIV infection is a key National Institutes of Health (NIH) research priority, which currently involves research across a number of areas. Combination antiretroviral therapy (cART) has radically changed the face of HIV infection by improving health, prolonging life, and substantially reducing the risk of HIV transmission.

Research toward a cure is a high priority for the NIH because of the continued risks for HIV-associated ill health even with effective cART use, and because the need for lifelong antiretroviral therapy (ART) is in itself a heavy burden on HIV-infected persons. The experience of Timothy Ray Brown, the so-called "Berlin Patient," has demonstrated that a cure for HIV infection is possible. Subsequent research has shown that cure or lifelong HIV remission will be a goal difficult to achieve. Yet the same research has demonstrated that prolonged and sustained HIV remission with concomitant absence of chronic immune activation is possible off therapy, even if cure or lifelong remission has not yet been achieved apart from in the case of the Berlin Patient. Better understanding is needed of the mechanisms and dynamics of HIV latency, persistence, reactivation, and reservoir formation in moving toward a therapeutic intervention that reliably and reproducibly results in a cure for HIV. Research on potential biomarkers for sustained viral remission and/or elimination, and biomarkers for incipient viral reactivation, among others, also are especially needed. Continued work on therapeutic interventions for inducing sustained viral remission is also vital.

The Initiative will help accelerate the ongoing development of drugs and cell and gene/gene modification-based therapeutic interventions that target persistent viral reservoirs in various cells, tissues, and organ systems, including the central nervous system. The NIH also will continue to support preclinical and clinical trials of innovative cure strategies, including those incorporating therapeutic vaccines and anti-HIV monoclonal antibodies.

FY 2016 RESEARCH PRIORITIES

- **Delineate the viral and host mechanisms directing persistence and latency, and the establishment and maintenance of viral reservoirs. Research is needed to answer the following questions:**
  - What are the mechanisms of establishment and maintenance of reservoirs?
  - What host cells and tissues contribute to the reservoir and/or to HIV persistence?
  - What are the molecular mechanisms that contribute to the establishment of latency and maintenance of latent infection, and of HIV provirus reactivation?
  - What is the transcriptional status of the latent proviruses *in vivo*? What host and viral factors modulate transcriptional status?
  - What is the role of tissue/organ system development/maturation in reservoir formation (e.g., reservoir formation in infancy)?
  - How soon after HIV infection acquisition are reservoirs established? Does this depend on risk behavior/practice, or route of transmission? Are there gender differences in the establishment and maintenance of the viral reservoir?
  - What is the contribution of cellular proliferation and cell-to-cell transmission in the maintenance of replication-competent viral reservoirs?
  - Does low-level viral replication despite effective ART exist? If so, does it contribute to persistence and latency?
  - Is persistence primarily driven by provirus latency, or by the quiescent state of the latently infected cell, or both?

- **Develop and test *in vitro,* small animal, nonhuman primate, and/or other nonhuman model systems that provide insight into the biology of HIV latency and persistence in humans.**
  - Develop and test model systems that enable the identification and preclinical characterization of potential cure interventions.
- **Identify and validate biomarkers, assays, and imaging techniques for research toward a cure. Research is needed to answer these questions:**
  - What should be the role of analytical antiretroviral treatment interruption (ATI) in the identification of promising cure treatment interventions?
  - What are the performance characteristics (sensitivity, specificity, precision, dynamic range) of biomarker assays needed or being used in cure research?
  - During ART, can the size of the replication-competent provirus population (reservoir) be measured using a readily accessible biomarker?
  - Are there biomarkers that can predict time-to-rebound during an ATI?
  - Are there pharmacokinetic differences by antiretroviral (ARV) agent or class that predict greater tissue penetration, decrease in viral reservoir size, and subsequent length of a successful ATI?
  - Will cure treatment-mediated changes in a biomarker predict changes in reservoir size and time-to-rebound during an ATI?
  - What are the optimal biomarkers for the pediatric and adult populations?
  - Can the reservoir be measured using small volume/small quantity samples?
  - Can noninvasive imaging methods be used to provide insights into anatomical distribution of reservoirs, as well as that of specific cell types, their metabolic state, and that of therapeutic agents?
- **Design and test novel approaches to control and/or eliminate viral reservoirs and persistent virus.**
  - Which HIV-infected cells give rise to rekindled infection during a planned ATI?
  - Can some or all of latent proviruses that constitute the relevant reservoirs be activated using latency-reversing agents?
  - Can all HIV-harboring cells be eliminated therapeutically?
  - Can the size of the reservoir be modified using immune-based intervention?
  - Do the pharmacokinetic characteristics and/or tissue penetration of certain ARV agents or classes modify the size of the reservoir?
  - Can hematopoietic stem cells and/or T cells be safely gene-modified to prevent HIV infection and/or HIV rebound in absence of therapy?

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE A: Basic Research—Biology of Reservoir Formation, HIV Latency, and Persistence. Delineate the viral, host, and pharmacokinetic/pharmacodynamic mechanisms that contribute to long-term persistence of replication-competent HIV during effective ART (the reservoir). Determine how latent infection is established, maintained, and potentially reversed. Identify factors involved in the generation and maintenance of the reservoir in diverse populations across the spectrum of age, gender, race, and/or ethnicity in domestic and international settings. This includes:

- Research on viral and host factors in the establishment and control of latent and/or persistent HIV
- Research on HIV replication and dissemination as a cause of persistence
- Research on cell proliferation and activation as a cause of persistence
- Research on the role of host immune dysfunction as a cause of persistence
- Research on the role of immune function and reservoir size in HIV cure/sustained remission
- Biomarkers, assay, and methods development.

OBJECTIVE B: Translational Research—Discover and Develop Strategies Targeted Toward a Cure for HIV Infection. Identify and validate viral and host factors and functions that can be targeted for cure/sustained remission of persistent virus. Discover and develop novel therapeutic strategies that may include therapeutic vaccines, other immunomodulatory interventions, and cell therapies that are effective solely or in combination in cure/sustained remission of HIV across the spectrum of age, gender, race, and/or ethnicity in domestic and international settings.

- Discover and develop safe and effective therapeutic agents and strategies to eradicate persistent, replication-competent HIV and/or induce long-term and complete suppression of HIV replication in the absence of ART.
- Discover and develop novel and safe cell therapy and gene therapy/gene modification methods to make and use cells resistant to HIV, or to prevent rebound viremia in the absence of therapy.
- Develop robust biomarkers that:
  - Measure the size of the reservoir;
  - Predict time-to-rebound during an analytical ATI; and/or
  - Predict response to cure interventions.

OBJECTIVE C: Conduct Clinical Studies of Strategies Capable of Cure/Sustained Remission of HIV. Assess the efficacy of therapeutic agents and novel strategies against persistent and latent virus. As these studies show progress, expand the scope to evaluate the interventions in HIV-infected individuals across the spectrum of age, gender, race, and/or ethnicity in domestic and international settings.

OBJECTIVE D: Behavioral and Social Science Research for HIV Cure. Support behavioral, social, structural, and cultural/environmental research to inform the development, testing, and implementation of HIV cure/sustained remission interventions; develop and test such interventions aimed at strengthening the reach and impact of HIV cure/sustained remission strategies across the spectrum of age, gender, race, and/or ethnicity in domestic and international settings.

OBJECTIVE E: Implementation Science for HIV Cure. Establish collaborations to strengthen the reach and availability of evidence-based HIV cure/sustained remission interventions across the spectrum of age, gender, race, and/or ethnicity in domestic and international, non-research, public health, and clinical care settings.

Women and Girls

Women represent more than 50 percent of the worldwide HIV epidemic. Women comprise 58 percent of people living with HIV in sub-Saharan Africa and 53 percent in the Caribbean. In 2013, almost 60 percent of all new HIV infections among young people aged 15–24 occurred among adolescent girls and young women. In the United States, African American women have an HIV prevalence rate nearly four times that of white women. African Americans and Hispanics represent 27 percent of all women in the United States, but they account for 79 percent of HIV cases among women.

Understanding the complexity of HIV in women requires studies that integrate the biological, behavioral, and social sciences to explain factors that influence HIV prevention, risk, pathogenesis, disease progression, and treatment outcomes in women and girls across the lifespan. The development of successful prevention and treatment interventions will need to consider how the context of women's lives influences effectiveness. Conducting this research in an environment of limited resources will mean encouraging collaboration among existing cohort studies, evaluating existing datasets and specimens, and considering carefully how new research initiatives will enhance knowledge about HIV in this population.

FY 2016 RESEARCH PRIORITIES

- **Examine the relationship of the female genital and anal/rectal tract microenvironment to HIV risk, prevention, acquisition, transmission, pathogenesis, and the establishment of viral reservoirs.** Female genital and anorectal tract immune function and the microbiome, including sexually transmitted infections (STIs) and bacterial vaginosis, are factors that can influence HIV in women. Other factors that need to be studied for their effect on HIV risk and infection in women include inflammation, endogenous and exogenous hormones, and injury from sexual violence.

- **Devise and study models of prevention for HIV and related coinfections and comorbidities that integrate biological approaches with the social and behavioral contexts of women's lives across the lifespan.** Recent data that demonstrate a linkage between human papillomavirus and HIV have renewed the debate about treating or preventing some STIs to facilitate HIV prevention. While animal models provide preliminary information about the biology of prevention, human studies in women have shown that understanding the social and behavioral factors that influence adherence to prevention intervention will inform the design of new prevention products and the successful implementation of current products. The development and study of multipurpose prevention technologies (MPTs) to prevent HIV and other STIs and/or pregnancy may mitigate the stigma associated with the use of HIV prevention products.

- **Design and study models of treatment and care for HIV and HIV-related coinfections and comorbidities that integrate biological approaches with the social and behavioral contexts of women's lives across the lifespan.** Women are lost from the HIV care continuum at rates similar to or greater than men. Understanding the underlying social and contextual issues that influence women's maintenance in HIV care can inform the development of successful care and treatment models that result in optimized health. Women's HIV outcomes may be improved through new models for HIV treatment and care that address women-specific conditions, comorbidities, and disease outcomes. Models that include effective preconception care approaches can optimize maternal health and prevent vertical and horizontal HIV transmission.

- **Conduct research on sex and gender identity differences in all aspects of HIV prevention, treatment, and care across the lifespan.** Differences in HIV between men and women, including transgender women, have not been well defined. Understanding these differences will inform effective approaches for HIV prevention and management in women. This research should include basic, behavioral and social science, and clinical and translational studies.

- **Study the impact of trauma and violence, including sexual violence, on HIV risk, acquisition, transmission, pathogenesis, care, and outcomes.** The influence of trauma and violence, including sexual violence, on HIV in women is not well understood. The social and behavioral impact of trauma on HIV in women has been described. The biologic effect of physical, sexual, and emotional trauma on immune function, and HIV risk, acquisition, and disease progression, has not been studied. Better understanding of this area of science will inform HIV risk, prevention, acquisition, and management research in women.

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: Determinants of HIV Acquisition/Transmission/Outcomes. Define the mechanisms by which biologic targets for intervention, host microbiota, and innate and adaptive immune factors influence HIV acquisition, transmission potential, pathogenesis, HIV reservoir, and treatment outcomes in women and girls across the lifespan.

OBJECTIVE–B: Integrated Biomedical, Behavioral, and Social Science Prevention Interventions. Conduct and support integrated biomedical, behavioral, and social science interventions research to prevent HIV acquisition in women, as well as transmission potential, including mother-to-child transmission.

OBJECTIVE–C: Biology of HIV Disease. Study the biology of HIV disease and related coinfections and comorbidities in women and girls across the life cycle.

OBJECTIVE–D: Treatment and Care of HIV Disease. Conduct and support research to inform the diagnosis and treatment of HIV-infected women and girls across the lifespan, including sex differences in ARV pharmacokinetics, pharmacodynamics, and disease outcomes, as well as the management of comorbidities related to both HIV disease and its therapy.

OBJECTIVE–E: Ethical Issues. Conduct and support research, training, and education on ethical issues that affect the access to and participation of women and girls in HIV-related research, including the emerging research agenda on HIV cure.

Racial and Ethnic Populations

Research on HIV as a health disparity continues to be essential given the disproportionate impact of HIV infection on racial, ethnic, and sexual minorities. These disparities affect not only the rates of HIV transmission and seroprevalence among these populations, but also treatment adherence, and by extension, treatment outcomes and HIV-associated morbidity and mortality.

Unraveling the complex interplay of factors (such as race, gender, and poverty) that affect HIV acquisition and transmission, as well as identifying individual-, community-, and population-level interventions, has been an important priority in the NIH AIDS research portfolio. However, specific populations continue to be underrepresented in NIH clinical research and among NIH-funded investigators.

FY 2016
RESEARCH
PRIORITIES

- **Stimulate greater research collaborations with tribal entities, as well as community-based organizations (and nontraditional community partners) to improve access to, as well as participation in, NIH-funded HIV research.** The areas of emphasis and objectives identified in this document emanate from the specific examination of the HIV epidemic among racial, ethnic, and sexual minority populations through a socioecological lens, with careful attention to not only the existing gaps in the NIH AIDS research portfolio, but also to the emerging observations and challenges in these populations that will continue to influence the study of the epidemic.

- **Identify the research needed to determine the effect of public health systems on the delivery of HIV services to racial, ethnic, and sexual minorities.** This will include attention to crosscutting research that spans a number of areas already contained in this document, such as behavioral and social science, therapeutics, and natural history and epidemiology.

- **Evaluate the effect of the changing health care system and marketplace (such as ARV rollover to generic formulations) on HIV-care-seeking behavior, care engagement, treatment outcomes, and retention.** In addition, the findings from the study of HIV infection among racial and ethnic minority communities have provided a base from which to explore complex societal and network interactions in HIV infection among other affected populations.

- **Determine what prevention approaches can both identity and modify the pathways through which specific social, contextual, and environmental factors interact with the goal of reducing HIV acquisition and transmission and disease progression across different populations and cultures.** Equally important is the study of HIV treatment in these populations, given the extent of comorbid conditions that affect not only ARV selection, but also the risk of treatment toxicity and overall effectiveness of ARV agents, including the risk of treatment nonadherence.

- **Investigate the genetic polymorphisms associated with ARV efficacy, tolerability, and toxicity to determine the effect of these on populations disproportionately affected by HIV infection, poor treatment outcomes, and high levels of HIV-associated morbidity.** Comorbidities also include the conditions that are often found at a higher prevalence in these populations, such as substance and alcohol abuse, mental health disorders, cardiovascular morbidity, metabolic disruptions, and daily struggles to meet the most basic of needs.

- **Promote multidisciplinary research to examine the complex interplay between HIV infection and the co-occurring comorbid conditions and circumstances that affect treatment selection, uptake, and adherence.** An emphasis on training investigators who reflect the populations disproportionately affected by the HIV epidemic remains a critically important aspect of the NIH AIDS research agenda. This training includes not only the standard clinical research tools necessary to conduct basic and clinical research, but also the skills required to explore the opportunities afforded by implementation science, social network analysis, and the creation of novel methodologies to adequately recruit and study very small populations, heretofore underrepresented in the NIH AIDS research portfolio.

- **Utilize implementation science to identify the human capital and financial costs necessary to scale up evidence-based interventions in disproportionately affected communities.** These priorities emanate from a series of questions, the answers to which will help to expand the understanding of HIV transmission, prevention, treatment, and its associated morbidities for many, but especially for those who disproportionately bear the burden of the epidemic.

- **Integrate community input into prevention research to identify key community-level factors that facilitate translation of evidence-based interventions into programs for disproportionately affected populations.**

FY 2016 RESEARCH OBJECTIVES

OBJECTIVE–A: System Determinants of Health. Conduct research that explores and identifies the impact that public health systems (such as health care, child welfare, and criminal justice) and financing structures have on the effective delivery of HIV-associated prevention, care, and treatment services to racial, ethnic, and sexual minority populations.

OBJECTIVE–B: Environmental and Social Determinants of Health. Conduct research that identifies specific social, contextual, and environmental factors—including, but not limited to, economic disadvantage, racism, sexism, transphobia, and homophobia—that are correlated with HIV acquisition, transmission, and disease progression.

OBJECTIVE–C: Community-Level Determinants of Health. Conduct research that explores community-level factors, such as community norms and neighborhood characteristics, that affect efficient and rapid translation, as well as implementation of evidence-based, cost-effective, and scalable community-level HIV interventions.

OBJECTIVE–D: Treatment and Treatment Access Disparities. Conduct research to identify and target the impediments to achieving optimal treatment outcomes in racial, ethnic, and sexual minority populations.

OBJECTIVE–E: Comorbidities. Conduct clinical, epidemiological, and basic science research to better understand the impact of race, ethnicity, and gender on the diagnosis, treatment, and management of disorders that frequently co-occur with HIV infection among ethnic, racial, and sexual minorities.

Research in International Settings

Research to address the global pandemic is essential. Since the early days of the epidemic, the NIH has maintained a strong international AIDS research portfolio that has grown to include projects in approximately 100 countries around the world. The NIH AIDS research studies are designed so that the results are relevant for both the host nation and the United States. These research programs also enhance 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. Global data demonstrate that the AIDS epidemic is manifested most dramatically in international settings, where resources often are limited and infrastructure may be less developed. At the same time, HIV demographics, risk factors, disease characteristics, comorbidities, and their impact are not uniformly distributed globally, and therefore research and interventions must be adapted to address the needs of communities most at risk or most affected by HIV.

FY 2016 RESEARCH PRIORITIES

- **Design and evaluate effective combinations of sustainable prevention approaches that integrate biomedical, sociobehavioral, and structural interventions tailored to specific international settings, epidemic conditions, and populations at risk to prevent HIV acquisition and transmission.** More research is needed to identify and evaluate the effectiveness of structural interventions in different international settings and at multiple levels, including individual, couple, group, and society. Continued attention also must be devoted to identifying HIV-related risk factors specific to diverse high-risk groups, while developing strategies to reduce these risks for HIV prevention. An additional challenge, particularly in low-resource settings, is the presence and synergistic interaction of concurrent and multiple risk factors (e.g., illicit substance and alcohol use, stigma, and low literacy). Of particular relevance in areas of the world where HIV incidence is highest, as in many international settings, HIV vaccine candidates that are suitable for diverse clades in different parts of the world are needed—with the ultimate aim of optimizing their properties for broad international use, including low cost, ease of production and administration, and stability.

- **Continue to develop and test effective ARV therapies and innovative strategies and interventions to make them available globally to successfully treat all persons with HIV and to cure HIV infection.** Internationally, multiple challenges remain in the use of current agents and therapeutic strategies at individual, community, and structural levels along the "care cascade" or treatment continuum. Significant gaps, attrition, and inequalities continue to exist at each step of the continuum, particularly in international settings; research on each of these steps is therefore essential.

  A particular challenge in many parts of the world is identifying individuals at the earliest/acute stages of recent HIV infection to more effectively implement "test and treat" strategies and thereby both effectively treat patients and interrupt transmission of the virus. A critical need is to identify barriers that prevent access to testing and develop strategies to reach those individuals. Equally important is conducting qualitative research to better understand individuals' perceptions of risk, which informs decisionmaking, while developing better strategies to mobilize individuals for testing.

  It is essential to continue to develop and ethically test new ARV agents, strategies, and formulations that will simplify treatment regimens and assure long-term adherence with minimal toxicity, affordable cost, and widespread availability—while evaluating and validating suitable and sustainable technologies for monitoring their effectiveness and safety.

  Finally, the early but evolving field of cure research presents a unique opportunity for participation by international researchers in cure strategy evaluation in their countries. They will be best suited to identify the large numbers of individuals and populations with acute infection globally required for cohort studies in basic, clinical, and sociobehavioral research.

- **Study the interactions among HIV-related comorbid conditions (e.g., coinfections and noncommunicable diseases, alcohol and substance use, and mental illness) in the context of the life cycle and unique to distinct international settings that affect HIV-related morbidity and mortality; develop and evaluate strategies for optimizing integrated and coordinated systems for diagnosis, prevention, and sustained care and treatment of these comorbidities and HIV.** It is well established that HIV infection affects and is influenced by a number of communicable and noncommunicable comorbid conditions. Although all comorbidities associated with HIV are represented in international settings, their distribution, incidence, prevalence, and the severity of their consequences differ in resource-limited settings compared with high-income areas of the world. This has been particularly true of the varied presence of communicable endemic diseases that are subsequently influenced by HIV immunosuppression.

  These HIV-related comorbidities in turn mediate and/or moderate HIV infection, affecting risk of acquisition, transmission, clinical characteristics, disease progression, and treatment outcomes. Tuberculosis (TB) and viral hepatitis remain the greatest causes of morbidity and mortality among HIV-infected individuals globally and require special attention. Other conditions have emerged more recently because of improved treatment and longer survival of HIV-infected individuals in many countries throughout the world, including in resource-limited settings. These conditions include malignancies, cardiovascular disease, neurological disorders, metabolic dysfunctions, and conditions associated with aging such as bone disease, cognitive decline, and frailty. It is critical to study these conditions in the context of HIV infection, and to integrate HIV prevention and treatment with the care for both communicable and noncommunicable comorbid conditions, while evaluating their impact across the lifespan.

  Particular emphasis must be placed on the major causes of morbidity and mortality among HIV-infected individuals in the global context, including:

  - Development and evaluation of new diagnostics, drugs, and regimens for more effective prevention, diagnosis, and treatment of coinfections associated with HIV, particularly TB, viral hepatitis, and STIs, is needed to optimize benefits and outcomes of both the comorbidity and HIV and to reduce adverse consequences of dual therapies, such as additive toxicities, drug resistance, or immune reconstitution syndromes.
  - The existence of multiple, preexisting, and concurrent comorbid conditions that increase risk of HIV and adversely affect treatment outcomes, such as mental illness and illicit substance and alcohol use, present difficult challenges in prevention and treatment, particularly in resource-limited settings. Integrated approaches must be developed and evaluated to improve prevention, diagnosis, and treatment strategies for these coexisting conditions.
  - Continued efforts are needed to design and test resource-appropriate technologies for improved screening, diagnosis, and management of cardiovascular and neurologic disease and malignancies, particularly oral, cervical, and anal cancers, and non-Hodgkin's lymphoma and Kaposi's sarcoma.

- **Expand translational research to enhance development of new HIV diagnostic, prevention, and therapeutic technologies, and strengthen implementation science to determine the impact and cost-effectiveness of existing interventions and strategy combinations; evaluate methods to improve their uptake and scale-up, and provide an evidence base to inform policies and practice in diverse international settings.** Translational research (from bench to bedside to community) and implementation science must be emphasized in the international HIV research agenda to facilitate movement from efficacy, to effectiveness, to scale-up and sustainability of interventions. Research approaches such as mathematical modeling and outcome studies that provide impact evaluation and cost-effectiveness analysis will help determine coverage levels, measure comparative impact, and facilitate evidence-based priority setting or decisionmaking between competing interventions in resource-limited settings.

  Clinical research should anticipate issues in the real-world implementation of new modalities for diagnostics, treatment, and prevention in clinical and community settings. The availability of these multiple modalities calls for the use of new adaptive research designs that enable optimization testing to better determine efficient, cost-effective protocols that can be delivered in commonplace settings.

Research is needed on enhancing the diffusion of research results and dissemination of new and existing technologies into effective prevention and care strategies. This includes evaluation of models for policy and program implementation, development of quality improvement systems, and evidence-based approaches to program adaptation in novel settings and populations.

FY 2016 RESEARCH OBJECTIVES

To optimize meaningful research results and ensure that research is conducted within the appropriate context for distinct international settings, the following objectives are incorporated across all of the priorities described above, in coordination and collaborative partnership with other U.S. Government, international, and multilateral organizations and programs. Particular effort is necessary to foster linkages among existing networks, with an emphasis on leveraging international sites with ongoing research activities and enhancing leadership and ownership by in-country researchers and communities.

OBJECTIVE–A: Foster a multidisciplinary and integrated approach utilizing basic, biomedical, behavioral, clinical, implementation science, and translational research, while taking into account local culture and customs and addressing multilevel challenges and sociodemographic factors. A life course perspective, with consideration of the entire family across the lifespan—from newborns and children to older adults—must be taken into account to examine differences over time related to risk perception and behavior, immune response and susceptibility to infection, disease characteristics and progression, drug pharmacokinetics, response and toxicity, and other factors.

OBJECTIVE–B: Study factors associated with social justice, inequity, and HIV-related health disparities—including, but not limited to, sexual orientation, substance use, gender/gender identity, ethnicity, poverty/food insecurity, low literacy, and intimate partner violence—along the continuum of HIV acquisition and transmission, diagnosis, prevention, care, and treatment. Special attention should be devoted to the contributing issue of stigma, discrimination, and criminalization of vulnerable or marginalized groups (such as individuals with drug and alcohol use disorders, persons engaging in transactional sex, orphaned children, or those from families affected by HIV), with a focus on developing effective methodologies for identifying these communities and identifying and testing potential interventions to reduce, and ultimately eliminate, these disparities and their negative impacts.

OBJECTIVE–C: Continue to strengthen research and public health capacity by building on existing efforts and developing new laboratory, clinical, and institutional infrastructure, while enhancing in-country research training, mentoring, and professional development. Particular emphasis should be placed on supporting the development of local scientific leadership to manage the difficult scientific questions; quality assurance systems and alternative technologies for rapid, reliable, and affordable diagnostics and treatment monitoring tools; and communication methodologies such as Web-based, mobile phone, and distance learning; strengthening capabilities in biostatistics; epidemiologic, clinical, and behavioral research; financial/grant management; and scientific and ethical reviews also should be emphasized.

Conclusion

Despite the groundbreaking scientific advances that have resulted from the NIH investment in AIDS research, many serious challenges lie ahead. There is little doubt that the AIDS pandemic will continue to affect virtually every nation in the world for decades to come. In light of this reality, the U.S. national commitment to AIDS research must remain strong. This Strategic Plan enables the NIH to build on this important moment in science and to define and prioritize critical research to find new tools that can turn the tide in the fight against this pandemic.

Appendices

Appendix A. Planning Groups

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Appendix B. OARAC Report to the NIH Director: Optimizing NIH HIV/AIDS Research in a Time of Budget Constraints

Date: May 28, 2014

To: Francis Collins, M.D., Ph.D., Director, NIH

Via: Jack Whitescarver, Ph.D., Associate Director for AIDS Research, NIH, and Director, Office of AIDS Research, NIH

From: Charles Carpenter, M.D., Chair, HIV/AIDS Research Portfolio Review Working Group
Rochelle Walensky, M.D., M.P.H., Chair, OAR Advisory Council (OARAC)

Subject: Science Priorities Report

On behalf of the members of the OARAC and its HIV/AIDS Research Portfolio Review Working Group (copied below), I am pleased to forward to you our final report outlining key science priorities for NIH HIV/AIDS research over the next 3 to 5 years. This report was prepared in response to your charge at the November 2013 OARAC meeting.

HIV/AIDS remains a critical component of the NIH research portfolio, as a number of scientific questions in HIV prevention, treatment, and co-morbidities remain to be answered before the pandemic can be abated in the U.S. and internationally. As our report makes clear, a robust, comprehensive, and integrated HIV/AIDS research portfolio at the NIH is essential for breaking down traditional silos, not only within the HIV arena (e.g., between prevention and treatment), but also between HIV and other health issues (e.g., other infectious and non-communicable diseases) to ensure better health outcomes for all. Continued investment in HIV/AIDS research will ensure that new discoveries with potential widespread impact occur and are translated and implemented in the most effective ways.

The charge to the OARAC was to identify the highest priority areas of HIV/AIDS research, which we have done; but we wish to make clear that we do not think these are the only important areas of science for the NIH to support. We hope that our recommendations will help guide the OAR, through its planning and budgeting authorities and in collaboration with the NIH Institutes and Centers and external stakeholders, to make optimal resource allocation decisions about AIDS-designated dollars in the coming years.

Thank you again for the opportunity to participate in this very important activity.

Cc:

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Optimizing NIH HIV/AIDS Research in a Time of Budget Constraints

Report of the HIV/AIDS Research Portfolio Review Working Group of the NIH Office of AIDS Research Advisory Council (OARAC) to the NIH Director

INTRODUCTION

Few other areas of NIH investment have paid off such dividends in discovery and health than those devoted over the last three decades to HIV/AIDS. Yet HIV/AIDS remains the most challenging and complex pandemic of this generation. Given that the pandemic remains poorly controlled both domestically and internationally, now is not the time to pull back on HIV/AIDS research; rather, it is time to capitalize on the critical advances achieved thus far in order to realize the shared vision of zero new infections and zero deaths caused by AIDS. Successes in prevention and treatment are still fragile and often unaffordable, so the job is not done. It is critical that the NIH pursue ever more promising discoveries in basic, clinical, behavioral, and social science research, including the development and testing of interventions based on these discoveries, to reach the ultimate goal shared by all—the end of AIDS and its attendant human suffering and economic costs.

An increasingly constrained budget poses a challenge for all aspects of the HIV/AIDS research response, and also requires a reassessment and focus of scarce resources on the highest priorities in the field—those that are most likely to have the greatest population-level impact in the near- and long-term. The OARAC Working Group appreciates the charge given by Dr. Collins to help identify these priorities for the NIH in core areas of HIV/AIDS research for the immediate future (the next 3 to 5 years).

We begin by articulating a few principles that inform our recommendations:

- HIV/AIDS research should emphasize prevention, care, and treatment strategies that have the greatest potential for population-level impact, focus on the most affected groups and settings, and address people across the life-course.
- Basic biomedical, behavioral, and social science underlies the identification, development, testing, and implementation of prevention, care, and treatment strategies.
- The most effective of these strategies are evidence-based, and evidence is best formulated when derived from multiple methods and sources.
- The implementation of a combination of multiple, evidence-based strategies appropriate to a particular setting is necessary to achieve desirable population-level outcomes.
- The co-occurring and intersecting biological, social, and environmental factors that influence HIV transmission, acquisition, pathogenesis, and treatment must be addressed simultaneously.
- HIV/AIDS research does not address just a single disease, but also the many co-infections and co-morbidities that occur in conjunction with HIV disease.
- HIV research has resulted in a multitude of crossover benefits for other disease and wellness areas, and, in some cases, those benefits in turn have influenced HIV-associated outcomes over time, thus creating a virtual cycle of research and its application.
- The conduct of the highest quality HIV research requires a robust pool of the highest quality researchers whose careers must be nurtured and supported at every stage through a commitment to training, infrastructure development, and capacity-building.
- Effective HIV research and its application and public health impact require collaboration among scientists, industry, governmental and non-governmental organizations, community-based organizations, policy-makers, patients, and advocates.

PRIORITIES AND RECOMMENDATIONS

The priorities and recommendations below are organized by discrete areas, but the Working Group wishes to emphasize that there is substantial overlap between them. Thus, in many places, we have interwoven into one area's priorities issues relevant to other areas in the report (e.g., basic science and behavioral and social science), as well as cross-cutting aspects of key population groups and innovative research methods. It is also important to note that the priorities are presented in no particular order (i.e., are not ranked), because they are all part of an interconnected, comprehensive approach to HIV/AIDS.

Prevention

Preventing new HIV infections remains the fundamental way to end AIDS. Because HIV is a transmissible disease, and infection occurs in the course of human relationships, it is essential to focus on both transmission and acquisition (i.e., both the infected and the uninfected persons) and the biological, behavioral, and social contexts in which these occur.

NIH should prioritize the following areas of research to prevent transmission and acquisition of HIV infection **focused on people/communities most at risk of/most affected by HIV in different locales:**

- Develop and test promising preventive and therapeutic vaccines and adjuvant candidates;
- Develop and test topical microbicides, microbicide/contraceptive combinations, and various methods of microbicide delivery that mitigate adherence issues;
- Develop and test pre-exposure prophylaxis (PrEP) candidates and methods of delivery that mitigate adherence issues;
- Conduct clinical trials and economic feasibility studies of promising candidates and approaches;
- Support trials assessing the effectiveness at a population level of integrated strategies for prevention of HIV infection; and
- Address behavioral and social/structural issues to increase access to, adoption of, and adherence to efficacious prevention methods.

It is essential that the NIH maintain its commitment to supporting a robust basic biomedical, behavioral, and social science program to support these HIV prevention (and related) priorities, and thus should:

- Support basic pathogenesis research and research in the non-human primate (NHP) and other animal models relevant to vaccine and microbicide development and identification of protection correlates.
- Support basic research on the immune system/immunology relevant to HIV prevention, including:
  - Innate immunity and viral restriction factors;
  - B and T cell immunology relevant to prophylactic vaccine development such as inducing broadly neutralizing antibodies, protective T cell responses;
  - Viral structure, immunogen design, vectors and delivery systems relevant to vaccine development; and
  - Mucosal immunity.
- Support basic behavioral and social sciences research to better identify, understand, and address social determinants and cultural drivers of HIV infection, resultant health disparities, and associated social stigma(s) in various settings.

Treatment: Anti-retroviral Therapy

Over the past two decades, there have been remarkable advances in treatment for HIV-infected persons that provide the foundation and set the stage for how to further improve current HIV therapy; optimally assess, manage, and prevent important co-infections and co-morbidities; extend the benefits of HIV treatment to all groups equitably; and, ultimately, cure HIV.

To advance this agenda, the NIH should prioritize HIV treatment research to develop and assess anti-retroviral drugs that are:

- More effective in suppressing viral replication at sites of virus production in tissues;
- More conveniently dosed;
- Less toxic;
- Able to achieve greater immunological reconstitution;
- More likely to avert the premature aging co-morbidities associated with immune activation; and
- More likely to achieve functional cure or eradication of infection.

The Prevention and Care Continua

NIH-supported research has demonstrated that anti-retroviral therapy is also effective in preventing transmission of HIV, thus solidifying the intertwining of prevention and treatment. In the U.S. and internationally, there continue to be significant gaps, attrition, and inequalities in the prevention and care continua, from HIV testing, to linkage to and engagement in services, to uptake of effective interventions, to adherence to effective regimens, to achievement of optimal health outcomes.

Thus, the NIH should prioritize inter- and multidisciplinary research to:

- Develop, test, and implement strategies to improve HIV testing, entry into prevention and treatment services, retention in these services, and achievement and maintenance of optimal prevention and treatment responses; and
- Address unique characteristics (e.g., gender, sexual orientation, race/ethnicity, age, geographic location, nutritional status, substance use, mental illness, socioeconomic status, acute infection, genetics, pregnancy status, history of violence and trauma, etc.) that influence individuals' experiences along the prevention and treatment continua.

Cure Research

Effective treatment has helped transform HIV from a usually fatal illness to a chronic and manageable disease, but one that remains largely incurable because of the persistence of HIV in latently infected cells and other reservoirs. However, recent evidence from a handful of individuals suggests that cure of HIV ultimately may be achievable. Curing HIV infection will have the associated benefits of people no longer needing life-long anti-retroviral treatment (with its attendant short- and long-term toxicities, adherence challenges, and cost), circumventing the adverse effects of HIV-1 persistence (including inappropriate immune activation, cardiovascular, central nervous system, and other end-organ damage), and reducing the potential risk for transmission and the ongoing stigma and discrimination associated with having HIV. Recent advances in cure research will be enhanced with further understanding of HIV persistence and development of new drugs and drug delivery mechanisms. The success of any cure strategy will be dependent on the ability and willingness of HIV-infected individuals to participate in clinical trials and, if efficacy of a cure method is ascertained, to use and adhere to it.

Thus, the NIH should prioritize research in the following areas:

- Animal models to understand viral pathogenesis and persistence and to test novel treatment strategies;
- HIV latency and reservoirs relevant to cure;
- Defining and measuring the reservoir;
- Maintaining/controlling the reservoir;
- Examining sex differences in the reservoir;
- Development and assessment of interventions aiming to cure HIV infection; and
- Assessment of acceptability and scalability of efficacious cure interventions and regulatory and ethical issues relevant to this research.

Co-Infections, Co-Morbidities, and Complications

It is well-established that HIV infection affects and is affected by co-occurring infections and co-morbid and non-communicable conditions. Among HIV-infected individuals, tuberculosis and hepatitis C infection are among the greatest causes of mortality, and the risk for co-morbidities such as cardiovascular disease, some cancers, bone fractures/osteoporosis, liver disease, kidney disease, cognitive decline, and aging-related frailty is higher than expected (i.e., relative to those without HIV infection). The direct study of multiple co-infections, co-morbidities, and complications in the context of HIV infection, disease, and treatment will expand understanding of root causes and expressions of disease that will benefit areas of NIH investigation other than HIV/AIDS. But, because most of these conditions also exist independent of HIV, the key question for the NIH is the appropriate allocation of dedicated AIDS dollars, as compared with non-AIDS dollars, to studies that address them. **The Working Group recommends that AIDS funding be reserved for research about these conditions and their manifestations only when they occur in the presence of HIV.**

With this in mind, the NIH should prioritize basic, clinical, behavioral, and social research to:

- Understand the effect of tuberculosis, malaria, cryptococcosis, and hepatitis B and C on HIV and the effect of HIV on these co-infections;
- Identify new diagnostics, treatment, and prevention methods for co-infections associated with HIV infection;
- Assess the significance of HIV complications and co-morbid conditions, including cardiovascular disease, kidney and liver disease, cancers, bone and muscle disease, metabolic diseases, neurologic diseases and disorders, and aging-associated frailty, in the context and throughout the life-course of HIV disease among all relevant age groups;
- Understand the role of chronic inflammation and immune activation in these co-infections and co-morbidities; and
- Understand the reciprocal operations and impact of HIV and co-occurring epidemics (e.g., other sexually transmitted infections, alcohol, tobacco, and drug use and addiction, violence and trauma, mental illness, etc.) in vulnerable populations.

Basic Science

Basic or foundational research encompasses a large and diverse area of science that cuts across key HIV/AIDS domains. Although the field has generated much knowledge to improve the current understanding of HIV virology and pathogenesis, significant gaps in understanding the interplay between the virus and host as well as the basic mechanisms involved in the host response to HIV remain.

In addition to the basic science emphasis required to address HIV prevention, treatment, co-morbidities, and cure noted above, the NIH should prioritize the following areas:

- Systems biology approaches and the development of new tools, standards, and methods to analyze data that can inform understanding of the host response to HIV infection and the phenotypic outcomes of HIV clinical trials and prevention strategies;
- Development of new methods to understand, measure, and improve drug delivery and drug metabolism in various compartments in the body and in different populations (e.g., men, women, children, and different races/ethnicities and national origins); and
- Development and use of animal models of HIV, SIV, and SHIV to understand viral pathogenesis and persistence, and to test novel treatment and prevention strategies.

Behavioral and Social Science

Employing a social-ecological framework to better understand and address simultaneously key individual, institutional, community, and social (including economic) factors that fuel or mitigate HIV epidemics in diverse populations and settings is essential to ending AIDS and associated health and social disparities.

Within this framework, and in addition to the behavioral and social science priorities attendant with HIV prevention, treatment, co-morbidities, and cure noted above, the NIH should prioritize the following areas:

- Innovative methods and frameworks to guide social and behavioral science interventions (e.g., adaptive interventions, new social media, mathematical modeling, economic value/policy impact/return on investment frameworks, etc.);
- Comparative effectiveness research; and
- Optimizing HIV prevention synergy (i.e., assessing the additive benefits of separately employed prevention interventions).

Implementation Science

Given that the NIH mission is "to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability," it is clear that implementation science is well within the agency's purview, and is complementary and can contribute to the program-implementing missions of other government agencies (e.g., CDC, HRSA, VA, IHS, SAMHSA, USAID, OGAC/PEPFAR).

In order for research to have the greatest impact on HIV in the U.S. and internationally—that is, to help move from efficacy, to effectiveness, to scale-up and sustainability—the NIH should prioritize implementation science related to addressing gaps in the HIV prevention and care continua.

Specifically, the NIH should support research to:

- Assess interventions and combinations of strategies to address obstacles to access to, uptake of, retention in, and scale-up and sustainability of efficacious, evidence-based HIV prevention, care, and treatment interventions in diverse U.S. and international settings.

Training, Infrastructure, and Capacity-Building

To ensure that the priority areas of HIV research noted above are addressed with novel and innovative approaches, the NIH must augment its commitment to early-career investigators and the people who mentor them. There are a number of mechanisms available through the NIH to support training, career development, and capacity-building, but often the funding levels are insufficient, and scientists from populations and communities most affected by the HIV epidemic are underrepresented as recipients of relevant awards.

The Working Group recommends that:

- As part of a broader review of the process and policy issue underlying the stewardship of the NIH AIDS research program mentioned below, attention be paid to the types, levels of support, and distribution of training, early career, and mentoring awards for both U.S. and international scholars.

Information Dissemination

The contributions and outcomes of NIH-supported AIDS research over the decades should quickly be made available and known by the American public in general and by all national and global stakeholders who have invested in it and benefitted from it. This extends to knowledge about the significant cross-over benefits of AIDS research to other areas of health and illness noted in this report. Moreover, a robust HIV/AIDS research information dissemination strategy is essential to the promotion of evidence-based and culturally competent practice.

To optimize the dissemination of HIV/AIDS research information, the NIH should:

- Support meetings and conferences in which the latest research findings are presented and exchanged among scientists, community members, patient advocates, industry representatives, policy-makers, program implementers, and the media; and
- Support research to enhance the public understanding of science, with HIV research and its crossover benefits as the example.

Process Issues for Managing the NIH HIV/AIDS Research Program

To optimize the scientific priorities identified in this report in an era of constrained resources, NIH HIV/AIDS research must be managed in the most effective and efficient ways possible. The NIH Office of AIDS Research (OAR) has been given unique statutory authorities by the U.S. Congress to act as the steward of HIV/AIDS research with respect to both scientific planning and priority-setting and the management of dedicated AIDS research funding. Yet, there are many processes more general to the NIH and its constituent Institutes, Centers, and other Operating Divisions, over which the OAR has little or no control and that influence what gets funded with AIDS research dollars and how. **While the Working Group was not charged with reviewing or making recommendations about these process issues, it wishes to highlight them and make the recommendation that they be addressed with relevant NIH research stakeholders.**

The goal of such an endeavor would be to identify steps along the grant solicitation, application, review, and award process at which the OAR could proactively exercise its needed influence to ensure that the highest priority HIV/AIDS research is funded with AIDS dollars. Critical engagement is required in the following steps:

- Approval of funding announcements (FOA, RFA, etc.);
- Review of HIV/AIDS-relatedness of grants submitted to the Center for Scientific Review (CSR);
- Assignment of grants to the Institutes and Centers;
- Determination of study section configuration and membership vis-à-vis appropriate expertise;
- Development of a trans-NIH definition, or set of criteria for what constitutes HIV/AIDS research;
- Development of a trans-NIH policy regarding proportional funding of grants and/or portfolios with AIDS dollars; and
- Assessment of training, mentoring, and capacity-building mechanisms for HIV/AIDS research.

CONCLUSION

The OARAC Working Group appreciates the opportunity afforded by Dr. Collins to provide our priorities and recommendations for optimizing the investment in AIDS research at NIH in the coming years. We recognize that the specific priorities we have articulated here are similar to what appears in the most current *Trans-NIH Plan for HIV-Related Research* and in reports from recent scientific workshops supported by the NIH and others. To a great extent this reflects the fact that the scientific planning processes led by the OAR as part of its mandate—in collaboration with the NIH Institutes and Centers and other national and international research organizations—are working. These processes regularly engage top minds across scientific disciplines, as well as community representatives, to assess developments in the epidemic and in research and to anticipate the most important and promising areas for further investment, and budget decisions guided by the OAR (also in collaboration with the Institutes and Centers) are informed by these deliberations.

At the same time, advances in HIV/AIDS science, the evolution of the epidemic, and the realization that dollars are tight call for a redoubling of effort to optimize the continued investment in HIV/AIDS research. This requires 1) evolving from the traditional "silos" by which the field has been organized categorically (e.g., biomedical versus behavioral, treatment versus prevention, basic versus clinical, etc.) toward a more integrated approach, and 2) undertaking a critical analysis of core institutional practices that influence the allocation of AIDS research dollars within the NIH that currently are beyond the control of the OAR.

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APPENDIX A: SNAPSHOT OF THE HIV/AIDS EPIDEMIC

Disease Burden: Prevalence/Incidence

Worldwide, HIV/AIDS remains a global scourge that affects people in nearly every country. According to UNAIDS, in 2012:

- More than 35.3 million people were estimated to be living with HIV/AIDS;
- 2.3 million were newly infected; and
- 1.6 million people died of AIDS-related illnesses, down from 2.3 million in 2005. Since the beginning of the epidemic, an estimated 36 million people have died of AIDS-related illnesses.

In the U.S., the HIV epidemic continues at an unacceptably high level. According to CDC:

- More than 1.1 million people are estimated to be HIV-infected; almost one in six (15.8%) of those people living with HIV is unaware of his/her infection, and it is estimated that 60% of those under age 25 are unaware of their infection.
- Approximately 50,000 new infections occur per year; the incidence of new infections has not declined for more than a decade.
- More than 636,000, cumulative AIDS deaths since the beginning of the epidemic; an estimated 15,529 people with AIDS died in 2010 (last year for which data is available).

Disease Burden: Affected Populations

Worldwide (UNAIDS data):

- The majority of cases worldwide are the result of heterosexual transmission.
- Women represent approximately 50% of all of those living with HIV infection, but that proportion is higher at 58% in sub-Saharan Africa.
- Global mother-to-child transmission rates in the absence of antiretroviral drug administration to the mother and infant are 15-30%, and increase to 45% with breastfeeding.
- Each day about 1,000 children—the majority of whom are newborns—become infected with HIV. An estimated 330,000 children became infected with HIV in 2011.
- 40% of all new adult HIV infections occur in 15–24 year olds.

In the U.S. (CDC Data):

- Men who have sex with men (MSM) and bisexual men of all races and ethnicities, African American men and women, and Hispanic MSM are the most affected groups.
- 63% of all new infections in 2010 occurred in MSM.
- In 2010, Blacks/African Americans accounted for 44% of all new infections, even though they comprise only 12% of the total U.S. population. Moreover, the new HIV infection rate among black men was more than six and a half times higher than for Caucasian men.
- At the end of 2010, Hispanics/Latinos represented 16% of the population but accounted for an estimated 19% of people living with HIV and 21% of new infections. The rate of new HIV infections among Hispanic/Latino men was more than two and a half times that of white men, and the rate among Hispanic/Latino women was nearly four and a half times that of white women.
- Persons aged 55 and older accounted for 19% of the estimated 1.1 million people living with HIV infection in the United States in 2010. Of the estimated 47,500 new HIV infections in 2010, 5% (2,500) were among Americans aged 55 and older.

- Among adolescents aged 13–19 years, 2,057 were diagnosed with HIV infection in 2009. 26% of new HIV infections are in 13–24 year olds.
- The rate of mother-to-child transmission of HIV in the United States has dropped from more than 25% to less than 2% during the last two decades, resulting in less than 100 cases per year.
- Heterosexuals and injection drug users continue to be affected by HIV. Individuals infected through heterosexual contact accounted for 25% of new HIV infections in 2010 and 27% of people living with HIV in 2009.
- As a group, women accounted for 20% of new HIV infections in 2010 and 24% of those living with HIV in 2009.
- Injection drug users represented 8% of new HIV infections in 2010 and 16% of those living with HIV in 2009. HIV/AIDS remains one of the most serious medical consequences of drug and alcohol abuse, and its link goes well beyond injection drug use to risky sexual behaviors brought on by intoxication or addiction (such as trading sex for drugs).
- Approximately 25% of HIV-infected individuals are also infected with HCV, a rate that increases to 80% among injection drug users.

APPENDIX B: SOURCES OF INPUT

The Working Group received input from OARAC members and invited speakers at the Council's November 14, 2013, and April 10, 2014, meetings.

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One of the key resources consulted by the Working Group during its deliberations was the *2015 Trans-NIH Plan for HIV-Related Research*, which had input from over 200 stakeholders, representing the NIH, academia, philanthropy, and community groups, organized in the following areas:

- Research Toward a Cure
- Racial and Ethnic Populations
- Natural History and Epidemiology
- Microbicides
- Research in International Settings
- Etiology and Pathogenesis
- Behavioral and Social Science Research
- Women and Girls
- Vaccine
- Therapeutics Research

The Working Group also received public comments from the following organizations:

- AIDS Action Baltimore
- AIDS Foundation of Chicago
- AIDS Treatment Activist Coalition
- American Psychological Association
- amfAR, The Foundation for AIDS Research
- AVAC: Global Advocacy for HIV Prevention
- Elizabeth Glazer Pediatric AIDS Foundation
- HIV Medicine Association
- HIV Prevention Justice Alliance
- National Minority AIDS Council
- Project Inform
- Treatment Action Group

APPENDIX C: THE TRANS-NIH AIDS RESEARCH PROGRAM

The NIH conducts and supports a comprehensive program of basic, clinical, translational, and behavioral research on HIV infection and its associated co-infections, opportunistic infections, malignancies, and other complications. AIDS research is coordinated by the Office of AIDS Research and carried out by all of the NIH Institutes and Centers (ICs), in both intramural and extramural programs.

NIH OFFICE OF AIDS RESEARCH

The Office of AIDS Research (OAR) (http://www.oar.nih.gov/), a component of the NIH Office of the Director, plans, coordinates, evaluates, and develops the priorities and budget for the NIH AIDS research program. AIDS research represents approximately 10 percent of the total NIH budget—the largest and most significant public investment in AIDS research in the world. Because HIV/AIDS so thoroughly transcends every area of clinical medicine and basic scientific investigation, every NIH Institute and Center plays a role in AIDS research. OAR identifies emerging scientific opportunities and public health challenges that require focused attention; manages and facilitates multi-Institute and trans-Institute activities to address those needs; fosters research by designating funds and supplements to pilot program areas; sponsors reviews or evaluations of research programs; facilitates international AIDS research and training; and supports initiatives to enhance dissemination of research findings to researchers, physicians, institutions, communities, constituency groups, and patients.

Strategic Planning Process: Each year, OAR develops the *Trans-NIH Plan for HIV-Related Research* in collaboration with the OAR Trans-NIH Coordinating Committees composed of intramural and extramural scientists, participants from other government agencies (CDC, USAID, FDA, VA, DoD, PEPFAR), non-government experts from academia and foundations, community representatives, and members of the OAR Advisory Council. During this process, the state of the science is reviewed; newly emerged and critical public health needs are assessed; and scientific opportunities are identified. The annual process identifies the scientific priorities that will have the highest impact on the pandemic in each of the scientific areas of the Plan. In addition, this year the OAR Advisory Council and a Working Group of the Council are undertaking a process to review and recommend the highest priorities in AIDS-related research.

Budget Development Process: The strategic Plan serves as the framework for developing the annual AIDS research budget. Each IC submits to OAR its request for AIDS-related research, presenting proposed new, expanded, or recompeting program initiatives, coded to specific objective(s) of the Plan. OAR builds each IC budget from the commitment base, allocating budgets to the ICs based on the priorities of the Plan, scientific opportunities, and the ICs' capacity to absorb and expend resources for the most meritorious science—not on a formula. This process reduces redundancy, promotes harmonization, and ensures cross-Institute collaboration. At the time of the appropriation, OAR informs each IC of its AIDS-related budget allocation, specifying amounts for each approved initiative. The ICs develop the funding announcements and approve/award the grants and projects.

Portfolio Analysis Process: A critical element of the annual process is a multi-tiered trans-NIH review of all grants and contracts supported with AIDS-designated funds due to expire or recompete in the coming fiscal year. OAR identifies those projects that are now considered of lower priority for their impact on AIDS research. ICs are informed that should these projects recompete successfully, they should not be funded with AIDS-designated dollars. Those funds will be used for higher priority AIDS research. This review ensures that the AIDS research budget is used to support the highest priority science, taking into account the changing clinical profile of the AIDS epidemic, as well as the evolving scientific priorities. This process has become an integral component of the annual strategic planning and budget development process.

KEY NIH INSTITUTES AND CENTERS CONDUCTING AIDS RESEARCH

National Cancer Institute (NCI)
The National Cancer Institute (NCI) supports and conducts a broad range of research on HIV/AIDS, with a focus on AIDS-associated and non-AIDS-defining malignancies. NCI scientists: Co-discovered HIV and proved that the virus caused AIDS; developed the first blood test for HIV, which permits diagnosis of the disease and ensures the safety of the blood supply; conducted clinical trials of the first AIDS drugs; and developed the technology for the first vaccine for human papillomavirus (HPV), which can protect against cervical cancer (an AIDS-defining cancer) and other cancers. While the development of anti-HIV therapy has lowered the incidence of AIDS-defining cancers substantially, the number of non-HIV-defining cancers has been increasing as people infected with HIV live longer and the HIV-infected population overall increases in age. Cancer is now one of the leading causes, if not the leading cause, of death for people infected with HIV. NCI supports a wide range of basic, translational, and clinical research on malignancies associated with HIV infection, including research initiatives to address the increasing number of AIDS-defining malignancies in the developing world.

National Eye Institute (NEI)
The National Eye Institute (NEI) of the NIH supports research on HIV-associated ophthalmic disorders, such as retinitis caused by infection by cytomegalovirus (CMV) infection, and potential therapies for these disorders. Blindness is one of the many complications of HIV infection and AIDS. NEI also supports studies on the possible development of ocular toxic effects related to the treatment of HIV infection, as well as research on ocular co-morbidities associated with HIV, such as herpes simplex virus.

National Heart, Lung, and Blood Institute (NHLBI)
As the HIV population ages, there has been a rise in the prevalence of chronic HIV-related cardiovascular, lung, and blood diseases. The mission of the National Heart, Lung, and Blood Institute (NHLBI) AIDS program is to support and facilitate research and training to address the emerging medical challenges facing the evolving HIV population. NHLBI is particularly interested in encouraging collaboration between HIV specialists and heart, lung, and blood specialists to further expand knowledge about HIV-associated coronary artery disease, heart failure, hypertension, sudden cardiac death, smoking cessation, chronic obstructive lung disease, and pulmonary hypertension.

National Institute on Aging (NIA)
The National Institute on Aging (NIA) at the NIH works to improve the care of older adults with HIV/AIDS. The increasing prevalence of HIV in older Americans is due in large part to the improved survival of individuals receiving therapy and to ongoing new infections in older adults. Older adults with HIV are at risk of developing a variety of comorbid conditions, including cardiovascular disease, dyslipidemia, insulin resistance, and diabetes. NIA research addresses aging-related factors that contribute to the pathogenesis, disease progression, treatment, quality of life, and access to care among older HIV-infected individuals.

National Institute on Alcohol Abuse and Alcoholism (NIAAA)
The National Institute on Alcohol Abuse and Alcoholism (NIAAA) supports epidemiologic, behavioral, and biomedical research exploring the complex and intertwined issues of alcohol abuse and HIV/AIDS. NIAAA supports research to: understand the ecology and clinical epidemiology of alcohol use, abuse, and dependence in HIV-infected populations; understand the role of alcohol in disease progression and premature mortality related to co-occurring disease processes such as organ and tissue inflammation and immune response; develop and test interventions to decrease risky sexual and substance use behaviors and disseminate interventions in a wide range of settings; and improve medication adherence in alcohol-using and -abusing HIV-infected persons.

National Institute of Allergy and Infectious Diseases (NIAID)
The National Institute of Allergy and Infectious Diseases (NIAID) is the largest federal institute for HIV/AIDS research. NIAID conducts and supports an extensive range of basic and clinical domestic and international research to: better understand HIV and how it causes disease; find new tools to prevent HIV infection including a preventive vaccine, microbicide, and treatment as prevention strategies; develop new and more effective treatments for people infected with HIV and related co-infections and co-morbidities; and conduct research that can one day lead to a cure for HIV infection.

A key component of the NIH intramural Program is the **Dale and Betty Bumpers Vaccine Research Center** (VRC). The primary focus of research is the development of vaccines for AIDS, but the VRC is also working on vaccines for other diseases, including Ebola, Marburg, and influenza. The VRC conducts a comprehensive program of research on the NIH intramural campus and works with scientists in academic, clinical, and industrial laboratories through a program of national and international collaborations. The potential scientific advances, methodologies, and resources will also provide the basis for research on vaccines for other diseases.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research on skin immunity and integrity and chronic diseases of muscle and bone related to HIV-associated comorbidities and inflammatory conditions. Advances in degenerative muscle and bone conditions are particularly relevant to an aging HIV-AIDS patient population. NIAMS-sponsored HIV-related research includes studies on: barrier and immune function in skin, which may provide important insights into the ability of HIV to enter the body through mucosal tissues and establish infection; the molecular mechanisms of muscle degeneration in HIV-infected and aging populations, and how it may be reversed; and the effects of HIV infection, ART, and aging on bones.

National Institute of Child Health and Human Development (NICHD)
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports and conducts research related to the unique features of HIV infection and AIDS in women, pregnant women, infants, children, adolescents, young adults, and families. Areas of focus for NICHD research include investigation of the biologic mechanisms of sexual transmission of HIV in the female genital tract; HIV interaction with endogenous and exogenous hormones; demographic and population-based studies related to sexual behavior; the interrelationship between HIV, pregnancy, and contraception; and research on HIV orphans and vulnerable children.

National Institute of Dental and Craniofacial Research (NIDCR)
The National Institute of Dental and Craniofacial Research (NIDCR) supports studies on the oral manifestations and oral malignancies of HIV/AIDS. HIV-related oral opportunistic infections, co-infections, and malignancies represent early diagnostic indicators of HIV infection, disease progression, immunosuppression, optimal or suboptimal therapies, drug resistance, and treatment compliance. The NIDCR AIDS and Immunosuppression Program supports global, basic, translational, and clinical research.

National Institute on Drug Abuse (NIDA)
The National Institute on Drug Abuse (NIDA) supports a broad range of research to reduce the spread of HIV among drug abusers and their partners and to minimize the associated health and social consequences of the disease both domestically and internationally. Drug and alcohol intoxication is linked with increased HIV risk behavior, and injection and non-injection drug use continues to contribute significantly to the spread of HIV.

National Institute of General Medical Sciences (NIGMS)
The National Institute of General Medical Sciences (NIGMS) supports research to answer critical scientific questions in cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, biomedical technology, bioinformatics, and computational biology, along with selected aspects of the behavioral sciences. NIGMS supports the structural characterization of HIV enzymes and viral proteins,

which has been instrumental in the development of antiretroviral drug therapies, such as protease inhibitors. NIGMS continues to support the characterization of viral proteins and is expanding its program to include cellular and viral complexes.

National Institute of Mental Health (NIMH)
The National Institute of Mental Health (NIMH) supports a broad range of AIDS-related research. NIMH sponsors studies on the basic neuroscience of HIV infection, including research to: elucidate the mechanisms underlying HIV-induced neuropath genesis; understand HIV-related motor and cognitive impairments; develop novel treatments to prevent or mitigate the neurobehavioral complications of HIV infection; and minimize the neurotoxicities induced by long-term use of antiretroviral therapy. Eradication of the virus from HIV-infected individuals to achieve a cure or a functional cure is a high research priority. NIMH behavioral science research targets prevention of HIV transmission and acquisition, adherence to interventions to reduce the burden of disease, and studies that address the behavioral consequences of HIV/AIDS.

National Institute of Neurological Disorders and Stroke (NINDS)
The National Institute of Neurological Disorders and Stroke (NINDS) supports basic, translational, and clinical research on the effects of chronic HIV infection and comorbidities on the central nervous system. NINDS-supported research includes studies of HIV-associated peripheral neuropathy; progressive multifocal leukoencephalopathy (PML); cryptococcal meningitis; cytomegalovirus infection; herpes virus infections; neuropathy; neurosyphilis; HIV-related psychological and neuropsychiatric disorders; and the effects of antiretroviral therapy on the nervous system. Studies to define and elucidate novel mechanisms of pathogenesis that are driving neurocognitive decline at the intersection of HIV-associated neurodegenerative processes, aging-associated central nervous system disease, chronic HAART treatment effects, and host susceptibility factors also are priorities.

National Institute of Nursing Research (NINR)
The National Institute of Nursing Research (NINR) sponsors domestic and international HIV/AIDS research focused on health promotion, disease prevention, and symptom management, including approaches to reduce HIV risk, develop and implement culturally appropriate HIV prevention education for adolescents; and overcome barriers to prevention in the U.S. and developing countries. NINR is focused on research to promote health and quality of life and prevention strategies across the course of HIV/AIDS disease, particularly in areas of symptom mechanism(s), biobehavioral interventions, prevalence disparity, age-related decision-making, and palliative and end-of-life care.

National Library of Medicine (NLM)
The National Library of Medicine (NLM) works to translate biomedical research into practice. NLM's electronic information services deliver trillions of bytes of data to millions of users, including scientists, health professionals, and the public in the U.S. and around the globe every day. NLM's information resources include AIDSinfo, a service of the U.S. Department of Health and Human Services (HHS), managed by NLM with support from OAR and NIAID, that offers access to the latest, federally approved HIV/AIDS medical practice guidelines, HIV treatment and prevention clinical trials, and other research information for health care providers, researchers, people affected by HIV/AIDS, and the general public. In addition, NLM supports MEDLINE®/PubMed®, PubMed Central®, MedlinePlus®, and Medline Plus en espanol. MedlinePlus includes a series of HIV/AIDS-specific pages in both English and Spanish. ClinicalTrials.gov provides the public with comprehensive information about all types of clinical research studies.

Center for Scientific Review (CSR)
The Center for Scientific Review (CSR) ensures that NIH grant applications receive fair, independent, expert, and timely reviews. CSR organizes peer review groups composed of experienced and respected researchers from across the country and abroad that evaluate the majority of NIH grant applications for their scientific merit.

These reviews allow NIH to fund the most scientifically promising research. All AIDS-related grant applications are reviewed by a study section or special emphasis panel within the AIDS and AIDS-Related Research [AARR] integrated review group, on an expedited cycle mandated by Congress. AARR reviews grant applications in the areas of basic, translational, clinical, and behavioral aspects of HIV/AIDS research.

Fogarty International Center (FIC)
The Fogarty International Center (FIC) is the NIH focal point for international cooperation in biomedical research, facilitating the global exchange of ideas and collaborative research. FIC builds partnerships between health research institutions in the U.S. and in low- and middle-income countries to support and facilitate basic, clinical, and applied research and research training for investigators interested in addressing the global HIV pandemic. With co-funding from other NIH Institutes, Centers, and Offices, FIC provides support to HIV-related research and to the development of multidisciplinary biomedical and behavioral and social science research capacity for the prevention, care, and treatment of HIV/AIDS and HIV-related conditions for adults and children in low- and middle-income countries. The Fogarty HIV Research Training Program strengthens the capacity of researchers and institutions in low- and middle-income countries to conduct HIV-related research in their countries and to compete independently for research funding.

Office of Research Infrastructure Programs (ORIP)
The Office of Research Infrastructure Programs (ORIP), a component of the Division of Program Coordination, Planning, and Strategic Initiatives in the NIH Office of the Director, supports the NIH's research infrastructure and research-related resources programs and coordinates the NIH's science education efforts. ORIP's infrastructure programs are designed to ensure that NIH effectively addresses and coordinates important areas of emerging scientific opportunities. The eight National Primate Research Centers (NPRCs) and other ORIP-funded primate resources provide comprehensive support for investigators engaged in HIV/AIDS research using nonhuman primates, including studies of mechanisms of pathogenesis and development of vaccines and microbicides. ORIP also funds cooperative agreements that support a consortium of specific pathogen free (SPF) macaque breeding colonies that provide animals to investigators studying many aspects of HIV/AIDS.

APPENDIX D: CHARGE TO THE OARAC

Office of AIDS Research Advisory Council
Charge from the NIH Director: Priority setting for NIH's AIDS research portfolio
November 14, 2013

AIDS Research is a critical component of NIH's portfolio. Current opportunities, from basic science to clinical trials, are rapidly evolving, and the possibility of an AIDS-free generation has emerged. Yet resources at NIH are significantly constrained – making it more important than ever for the NIH to establish and implement AIDS research priorities to maximize the chances of progress.

The Office of AIDS Research (OAR) carries the responsibility of overseeing the allocation of funds for this program. For that mandate to be optimally implemented at a time of such rapid progress in AIDS research, it is timely to develop a top level enumeration of research priorities that can be utilized to guide the optimum investment of the roughly 10% of the NIH budget allocated to AIDS research.

Accordingly, the Office of AIDS Research Advisory Council (OARAC) is charged with developing a blueprint that identifies AIDS research priorities over the next 3 – 5 years. This should be bold but achievable; specific enough to guide decision making but avoiding over-granularity; comprehensive in its consideration of the broad sweep of AIDS research but courageous in identifying major priorities and recognizing that a laundry list of every conceivable AIDS-related program will not be very useful.

While the OARAC may choose to produce a background white paper that summarizes current research opportunities, the most critical part of the document should be an Executive Summary of no more than four pages. This should outline the highest priority AIDS research in three areas:

- Prevention – including vaccines, microbicides, ARV-based prevention, behavioral research focused on risk reduction, stigma, and adherence
- Treatment – including advances in therapeutic interventions and research toward a cure
- Co-morbidities – neurologic, cardiovascular, oncologic, accelerated aging

The document should also identify high priority research in three areas that cut across these themes – basic science, training (including capacity building), and information dissemination.

The OARAC may use whatever means necessary to obtain expert input to guide their conclusions. The OAR will provide staff support for this effort. A draft document should be generated by spring of 2014, and should then be made broadly available for public comment. Based on those comments, a revised version should be compiled and presented to the Advisory Committee to the Director (ACD) at their June 2014 meeting.

Francis S. Collins, M.D.,Ph.D.
Director, NIH

Appendix C. NIH AIDS Research Information Resources

- **Office of AIDS Research** . . . . . *http://www.oar.nih.gov*
  Coordinates the scientific, budgetary, legislative, and policy elements of the National Institutes of Health (NIH) AIDS research program.

- **NIH AIDS Research Information** . . . . . *http://health.nih.gov/topic/AIDS*
  AIDS research fact sheets and updates from the Institutes and Centers leading the National Institutes of Health AIDS research agenda.

- **National Institute of Allergy and Infectious Diseases (NIAID) AIDS Research Information** . . . . . *http://www.niaid.nih.gov/topics/hivaids*
  Research updates from NIAID at the National Institutes of Health.

- **AIDS*info*** . . . . . *http://www.aidsinfo.nih.gov*
  The latest information and resources on HIV/AIDS research, clinical trials, Federal treatment guidelines, and HIV-related therapies.

- **National Library of Medicine HIV/AIDS Information** . . . . . *http://aids.nlm.nih.gov*
  AIDS resources from the world's largest medical library at the National Institutes of Health.

- **PubMed** . . . . . *http://www.ncbi.nlm.nih.gov/pubmed*
  Searchable resource of more than 21 million citations for biomedical literature.

- **NIH Information** . . . . . *http://www.nih.gov*
  The official Web site of the National Institutes of Health.

- **AIDS.gov** . . . . . *http://www.aids.gov*
  HIV/AIDS information from the U.S. Government.

Appendix D. NIH Institutes and Centers

NCI . . . . . National Cancer Institute

NEI . . . . . National Eye Institute

NHLBI . . . . National Heart, Lung, and Blood Institute

NHGRI . . . . National Human Genome Research Institute

NIA . . . . . National Institute on Aging

NIAAA. . . . . National Institute on Alcohol Abuse and Alcoholism

NIAID . . . . . National Institute of Allergy and Infectious Diseases

NIAMS . . . . National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIBIB . . . . . National Institute of Biomedical Imaging and Bioengineering

NICHD . . . . *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NIDCD . . . . National Institute on Deafness and Other Communication Disorders

NIDCR. . . . . National Institute of Dental and Craniofacial Research

NIDDK. . . . . National Institute of Diabetes and Digestive and Kidney Diseases

NIDA. . . . . National Institute on Drug Abuse

NIEHS. . . . . National Institute of Environmental Health Sciences

NIGMS . . . . National Institute of General Medical Sciences

NIMH . . . . . National Institute of Mental Health

NIMHD . . . . National Institute on Minority Health and Health Disparities

NINDS. . . . . National Institute of Neurological Disorders and Stroke

NINR. . . . . National Institute of Nursing Research

NLM . . . . . National Library of Medicine

CIT . . . . . Center for Information Technology

CSR. . . . . Center for Scientific Review

FIC . . . . . Fogarty International Center

NCCIH . . . . National Center for Complementary and Integrative Health

NCATS . . . . National Center for Advancing Translational Sciences

CC. . . . . NIH Clinical Center

Appendix E. List of Acronyms

AIDS . . . . . acquired immunodeficiency syndrome

ART. . . . . antiretroviral therapy

ARV. . . . . antiretroviral

ATI . . . . . antiretroviral treatment interruption

cART. . . . . combination antiretroviral therapy

CDC . . . . . Centers for Disease Control and Prevention

EHR . . . . . electronic health record

HBV . . . . . hepatitis B virus

HCV . . . . . hepatitis C virus

HIV . . . . . human immunodeficiency virus

ICs . . . . . Institutes and Centers

KSHV . . . . . Kaposi's sarcoma-associated herpesvirus

MPTs. . . . . multipurpose prevention technologies

MSM . . . . . men who have sex with men

MTCT . . . . . mother-to-child transmission

NCD . . . . . noncommunicable disease

NGO . . . . . nongovernmental organization

NIH . . . . . National Institutes of Health

OAR . . . . . Office of AIDS Research, NIH

OI . . . . . opportunistic infection

PD. . . . . pharmacodynamic(s)

PK. . . . . pharmacokinetic(s)

PrEP . . . . . pre-exposure prophylaxis

RCDC . . . . . Research, Condition, and Disease Categorization

SHIV . . . . . chimeric simian/human immunodeficiency virus

SIV . . . . . simian immunodeficiency virus

STI . . . . . sexually transmitted infection

TB . . . . . tuberculosis

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