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Fiscal Year 2023 NIH HIV/AIDS Professional Judgment Budget Focus on the Future





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The FY 2023 Professional Judgment Budget estimate will allow NIH to expand HIV science in focused priority areas of research.





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Director's Message

In the 40 years since the first cases of AIDS were reported, the persistent dedication of researchers, global activists, public health officials, and private sector partners has helped reduce new HIV infections globally and transformed HIV and AIDS from a fatal disease into a manageable chronic condition. Much of this success—in the United States and globally—is due to ongoing investments by the National Institutes of Health (NIH) in the development, evaluation, and implementation of highly effective HIV prevention and treatment strategies.

Just recently, for example, NIH-supported research in partnership with industry helped demonstrate the safety and efficacy of long-acting formulations of antiretroviral drugs for HIV treatment and prevention. As a result, in 2021, the U.S. Food and Drug Administration (FDA) approved two long-acting injectable formulations that hold promise for improving adherence to antiretroviral treatment (ART) regimens for people with and at risk of HIV for whom daily pill-taking is not feasible.

NIH investments in HIV/AIDS research had a significant global impact during the SARS-CoV-2 pandemic. Findings from basic HIV research, infrastructure, and partnerships developed in the pursuit of HIV prevention and treatment strategies have proven to be foundational to the COVID-19 response, particularly by accelerating the development of new vaccines and therapies to combat the SARS-CoV-2 infection. The messenger RNA (mRNA) and adenovirus platforms that were under investigation for the development of HIV vaccine candidates led to the successful development of safe and effective COVID-19 vaccines in record time.¹ This is a stellar example of the crossover benefits of NIH investment in HIV/AIDS research.

Globally, about 38 million people are living with HIV, and more than 1.5 million new infections occur each year. It is clear that much work needs to be done to control and, ultimately, end the HIV/AIDS pandemic. While we have made tremendous strides in HIV basic, clinical, translational, behavioral, social, and implementation science, core questions remain to be answered. In basic science, for example, the nuances of HIV viral–host cell interactions and the mechanisms of HIV persistence in body tissues, even in persons treated with ART who have undetectable viral loads, are not fully understood. Likewise, in social science, the causal pathways through which social factors—such as stigma, racism, poverty, food and housing insecurity, and under-capacitated health systems—operate and continue to confer differential risk among communities have not been fully characterized.

The Fiscal Year (FY) 2022 Omnibus Bill signed into law on March 15, 2022, provided the NIH Office of AIDS Research (OAR) with an increase of \$104 million (3.4% over FY 2021) for distribution across the NIH Institutes, Centers, and Offices (ICOs). This is the largest increase for HIV/AIDS research since FY 2014, and the amount represents 13.4 percent of the \$775 million increase requested in the FY 2022 Professional Judgment Budget. Research areas benefitting from the additional funding increase include HIV vaccines, long-acting treatment strategies and prevention tools, HIV cure, neurologic complications of HIV infection across the lifespan, disparities and stigma, implementation research, and HIV workforce expansion and diversification.

To build on recent developments in these areas and to address current and emerging needs, the FY 2023 Professional Judgment Budget requests \$639 million in additional funds, a 20 percent increase in the HIV/AIDS research investment over the FY 2022 Enacted Level.

Funding at this level will allow NIH to further unravel the complexities of the viral life cycle, develop an HIV vaccine (or vaccines) and more effective drug therapies, address the impact of key HIV coinfections, redress HIV-associated health disparities, and eventually find an HIV cure. In addition, increased resources will accelerate the pipelines of novel and effective HIV prevention and treatment products and identify optimal ways to ensure access to them among communities most in need, ensure a diverse pool of HIV investigators, and expand partnerships with stakeholders both inside and outside of government to strengthen the links between science, practice, and policy.

The HIV/AIDS Professional Judgment Budget estimates the amount of additional funds that are necessary during FY 2023 to address the goals of the *FY 2021–2025 NIH Strategic Plan for HIV and HIV-Related Research* (the NIH Plan).² Working with our governmental, professional, and civil society partners also will accelerate the implementation of NIH HIV/AIDS research contributions to the FY 2022–2025 U.S. *National HIV/AIDS Strategy* (NHAS)³ and the *Ending the HIV Epidemic in the U.S.* (EHE)⁴ initiative to halt new HIV transmissions and to improve the lives of people with and affected by HIV in the United States and globally.

NIH is working with governmental, professional, and civil society partners to implement the *NIH FY 2021–2025 NIH Strategic Plan for HIV and HIV-Related Research* and accelerate the NIH HIV/AIDS research contributions to the FY 2022–2025 U.S. *National HIV/AIDS Strategy* (NHAS) and the *Ending the HIV Epidemic in the U.S.* (EHE) initiative to halt new HIV transmissions and improve the lives of people with and affected by HIV in the United States and globally.



Introduction

HIV continues to be one of the world's most significant public health and economic development challenges. Globally, 79 million people have been infected with HIV since the beginning of the HIV/ AIDS pandemic in 1981, and more than 36 million have died. Currently, approximately 38 million people around the world are living with HIV. New infections declined by 52 percent from peak levels in 1997, but still about 1.5 million people acquired HIV in 2020. Globally in 2019, among people with HIV, about 81 percent knew their HIV status, 67 percent were accessing treatment, and 59 percent were virally suppressed.⁵

In the United States, at the end of 2019, an estimated 1.2 million Americans were living with HIV, including almost 160,000 individuals who were unaware of their infection. Even though new HIV diagnoses trended downward by 9 percent between 2015 and 2019, about 38,000 new HIV diagnoses still were reported in 2019. Among all adults and adolescents with HIV, approximately 87 percent were aware of their HIV status, 66 percent received some HIV care, 50 percent were retained in care, and 57 percent achieved viral suppression.⁶

HIV prevalence and incidence are distributed unequally, reflecting ongoing disparities related to race, ethnicity, sex, gender, age, socioeconomic status, and geographic region. Such disparities affect the ability of people to know about and to access HIV services that fit their needs and were exacerbated by the impact of the COVID-19 pandemic. Evidence is mounting that the pandemic has reduced HIV testing, linkage to care, and access to treatment, resulting in increases in HIV incidence, prevalence, and mortality. For example, The Global Fund to Fight AIDS, Tuberculosis and Malaria reported that HIV testing declined 41 percent and referrals for diagnosis and treatment declined by 37 percent in African and Asian countries during the first COVID-19 lockdowns in 2020 compared with the same period in 2019.⁷

The COVID-19 pandemic continues to have significant impact on the HIV/AIDS research enterprise. Basic and translational research unrelated to SARS-CoV-2 and COVID-19 in academic settings was suspended for months, severely delaying progress for trainees and principal investigators.^{8,9,10} Health care workers and clinical researchers were diverted to the care of COVID-19 patients, while clinical research resources were redirected to treatment and care for those with COVID-19. Recruitment and staffing for HIV and other clinical trials were halted due to social distancing, travel restrictions, and lockdown measures.

Notwithstanding the disruptions to research, public health services, and medical care due to the global COVID-19 pandemic, there have been exciting scientific advances in recent years. These include the demonstration of the safety and efficacy of long-acting formulations of antiretroviral drugs for both pre-exposure prophylaxis (PrEP) and treatment,^{11,12} the design of a new class of therapeutics—capsid inhibitors—targeting a new aspect of the HIV viral life cycle,¹³ and the testing of CRISPR-based gene-therapy approaches in HIV cure research.¹⁴ These advances emanate from the cumulative knowledge of four decades of HIV/AIDS research and point to exciting new directions that provide even greater promise for ending the HIV/AIDS epidemic in the United States and globally.

Rapid pivots to new research directions require additional resources. The experience of the COVID-19 pandemic has taught us that with concerted investment and strong partnerships among stakeholders, it is possible to create new, faster, and more effective ways to advance discovery and translate outcomes to public health implementation. Importantly, the response to the COVID-19 pandemic demonstrates the crossover benefits of HIV/AIDS research, which proved foundational to the pursuit and development of COVID-19 vaccines and treatments that, in turn, are informing HIV/AIDS research. Now is the time to capitalize on the bidirectional lessons learned during the COVID-19 pandemic and honor the commitment to end the global HIV/AIDS epidemic.

Budgets, Funding, and Resources Needed

Over the past 3 fiscal years (2019–2021), the NIH HIV/AIDS research budget increased only modestly following 4 years (2015–2018) of flat funding. During this 7-year period, the budget lagged behind the increases in costs associated with conducting critical HIV/AIDS research (see **Figure 1**).



Figure 1. Effect of Inflation on Research Purchasing Power

Note: NIH funding does not include COVID-19 appropriations. Source: Biomedical Research and Development Price Index (BRDPI).



The FY 2022 Omnibus bill provided the NIH OAR "no less than \$3,194,000,000 for HIV/AIDS research across NIH," an increase of \$104 million (3.4%) over the FY 2021 enacted budget level.

The increase represents the equivalent of 13.4 percent of the \$775 million requested in the FY 2022 Professional Judgment Budget and is the largest increase for NIH HIV/AIDS research since 2014, providing funding to build on new opportunities to end the HIV/AIDS pandemic globally and in the United States.

In contrast to the first 15 years of the HIV/AIDS pandemic, people with HIV now are living longer but experiencing more comorbidities associated with HIV and long-term antiretroviral treatment (ART). This development is opening up new areas of research at the intersection of HIV and aging, which, in turn, is increasing the overall scope of and required resources for the NIH HIV/AIDS research portfolio. Strengthening the HIV/AIDS research investment now is critical to provide better life quality and prevent premature mortality for people aging with HIV, as well as reduce future health care costs.

NIH OAR presents the Professional Judgment Budget estimate in accordance with The NIH Revitalization Act of 1993,¹⁵ which authorized OAR to plan, coordinate, and evaluate HIV/AIDS research conducted or supported across the NIH. The HIV/AIDS Professional Judgment Budget highlights accomplishments in HIV/AIDS research during the prior year and estimates the investment needed to advance progress in priority areas of science "without regard to the probability that such amounts will be appropriated." The Professional Judgment Budget builds on the justification to Congress for the President's Budget.

The proposed FY 2023 Professional Judgment Budget for the NIH-wide HIV/AIDS research program is \$3.833 billion, an increase of \$639 million, or 20 percent, over the FY 2022 Enacted Level (see **Table 1**). The budget estimates the resources needed to optimize recent and exciting discoveries in HIV/AIDS research, ensure a robust pipeline of diverse HIV investigators, and correct some of the accumulated decreased spending power.

Overarching Research Priority	FY 2022 (Enacted)	Estimated Increase*	FY 2023 Professional Judgment Total
Reduce the Incidence of HIV	\$693,528	\$153,312	\$846,840
Develop Next-Generation Therapies	358,309	63,044	421,353
Research Toward a Cure	218,347	64,716	283,063
Address HIV-Associated Comorbidities, Coinfections, and Complications	582,792	114,984	697,776
Cross-Cutting Areas**	1,341,024	242,744	1,583,768
Total	\$3,194,000	\$638,800	\$3,832,800

Table 1. FY 2023 HIV/AIDS Professional Judgment Budget Request (Dollars in Thousands)

*Projected distribution of estimated increase across research priorities

**Cross-cutting areas include basic science, behavioral and social science, epidemiology, health disparities, implementation science, information dissemination, and research training.

The focus of the estimated Professional Judgment Budget is displayed in accordance with the overarching NIH HIV/AIDS research priorities described in the NIH Plan (**Figure 2**). One of the unique features of the OAR is its mandate to allocate and manage the NIH HIV/AIDS research budget, in collaboration with the NIH ICOs, which carry out and administer the HIV/AIDS research and training programs, in alignment with the Plan's priorities.

Figure 2. FY 2023 NIH OAR Professional Judgment Priorities for HIV and HIV-Related Research

Reduce the Incidence of HIV

- Accelerate testing of promising HIV vaccines approaches utilizing mRNA and selfamplifying RNA (saRNA) delivery technologies and structure-based designer antigens.
- > Extend the repertoire of long-acting formulations for pre-exposure prophylaxis (PrEP) and for antibody-mediated approaches for HIV prevention.

Develop Next-Generation Therapies

- > Develop and implement technology for novel testing strategies to measure the effectiveness of treatments to sustain viral suppression and eradicate viral replication in all cellular reservoirs.
- > Enhance the assessment of the acceptability and effectiveness of new technologies such as long-acting injectables, implants, microarray patches, and vaginal rings—to diversify delivery options for HIV therapeutic interventions.



Research Toward a Cure

- Develop and implement novel technologies to better understand genomic and epigenetic features of viral integration sites and to characterize and control viral reservoirs in different cell types.
- Test the efficacy of novel cure strategies in appropriate animal models and human clinical trials.

Address HIV-Associated Comorbidities, Coinfections, and Complications

- Develop interdisciplinary approaches to study the intersection among biological, pathophysiological, and psychosocial factors that affect health outcomes in people living and aging with HIV.
- > Address the interplay of HIV and SARS-CoV-2 coinfection on HIV pathogenesis.

Cross-Cutting Areas

- > Basic Science: Expand understanding of the virus lifecycle by imaging and modeling to inform the development of next-generation HIV therapies with new targets.
- > Behavioral, Social, and Implementation Sciences: Expand understanding of the causal pathways between core psychosocial factors and HIV outcomes, including health disparities and inequalities, to inform development of social–structural interventions and develop appropriate metrics and methodologies for assessing health systems, organizational contexts, and implementation processes and outcomes in diverse settings.
- Training, Capacity-Building, and Infrastructure: Expand the pool of diverse earlycareer HIV investigators, particularly those from underrepresented groups and underresourced institutions.

Scientific Advances and Opportunities

In recent years, NIH investments in HIV/AIDS research have produced novel approaches, tools, methods, discoveries, and outcomes that cut across scientific disciplines and reflect the input of multiple stakeholders. Additional resources are essential to capitalize on these advances and stimulate further innovation in four areas that traverse NIH HIV/AIDS research priorities and NIH Plan Strategic Goals (**Figure 3**):



- 1. Expand basic research in biomedical, behavioral, and social sciences.
- 2. Address leading co-occurring conditions.
- 3. Develop and apply transformative technologies, methodologies, and implementation approaches.
- 4. Enhance diversity and strengthen capacity in the HIV/AIDS research workforce.

Figure 3: NIH Plan Strategic Goals



Strategic Goal 1:

Advance rigorous and innovative research to end the HIV pandemic and improve the health of people with, at risk for, or affected by HIV across the lifespan.

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Strategic Goal 2:

Ensure that the NIH HIV research portfolio remains flexible and responsive to emerging scientific opportunities and discoveries.

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Strategic Goal 3:

Promote dissemination and implementation of research discoveries for public health impact across agencies, departments, and stakeholders within the U.S. Government and globally.

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Strategic Goal 4:

Build human resource and infrastructure capacity to enhance sustainability of HIV research discovery and the implementation of findings by a diverse and multidisciplinary workforce.





Back to Basics

NIH investments in HIV and AIDS research over 4 decades have produced groundbreaking advances in understanding the basic virology, immunology, and pathogenesis of HIV. Yet there still is no vaccine to prevent HIV infection; the virus persists in reservoirs in people with HIV who are on highly effective antiretroviral therapy; and people aging with HIV are a growing population with a new comorbidities that can contribute to reduced quality of life and premature mortality.

Similarly, historic NIH investments in HIV-related basic behavioral and social research have produced important advances in understanding fundamental psychological and social–structural factors that contribute to increased risk or protection from HIV and its consequences for different individuals and groups. Yet HIV transmission through sexual and drug-using activities continues at alarming rates; sex, gender, race, ethnic, age, economic, and geographic disparities in HIV acquisition, treatment, and support persist; and these disparities position people and groups to be similarly vulnerable to other pandemics, as seen with COVID-19.

These realities point to the need to invest greater resources in basic biomedical, behavioral, and social research to better understand the pathways and mechanisms of HIV replication and to develop effective, community-appropriate, people-centered interventions to prevent or manage HIV infection.

Basic Biomedical Research

The unusual characteristics of the HIV viral life cycle present unprecedented challenges to the development of effective vaccine and cure strategies. Further investment is needed in basic virology, immunology, and systems biology that is relevant to developing safe and effective vaccines and therapeutics, combatting drug-resistant viruses, and crafting HIV remission and cure strategies that address both virus elimination and suppression of virus replication. Critical gaps persist in understanding the fundamental aspects of innate immunity, cell type contribution to the HIV reservoirs, and host genetic factors, all of which may influence the size, location, and composition of latent reservoirs in people with HIV on ART.

Basic, clinical, and translational research to evaluate the human immune response to an HIV vaccine remains a critical priority. Advances in imaging technologies have led to the development of vaccine candidates that more closely mimic structural components of the HIV envelope and could provide the foundation for improved vaccines to induce protective immunity.

Fundamental research in pathophysiology relevant to understanding comorbidities commonly occurring with HIV and the effects of long-term ART use is essential to improve the well-being of people with HIV over the life course. Underlying pathogenesis and mechanisms of HIV-associated comorbidities, coinfections, and complications (CCCs) that involve multiple systems may be different along the lifespan for persons with HIV as compared with those without HIV. Similarly, specific phenotypes, indicators, and biomarkers associated with CCCs will likely be unique to people with HIV.^{16,17,18} Among the overlapping etiologies and pathogenic mechanisms of CCCs are factors that drive chronic immune activation and dysfunction among people on ART; shared immune pathways and microbiome/virome contributions toward inflammation/chronic immune activation and immune dysfunction; and mechanisms that drive accentuated aging.^{19,20,21} New research approaches are needed to better understand and address HIV-associated CCCs across the lifespan.

Basic Behavioral and Social Science

Progress in HIV prevention, treatment, and cure—even with the best biomedical advances is affected by numerous social factors that influence knowledge, attitudes, availability, uptake, and adherence among individuals and groups. These social factors and determinants shape the environment in which individuals interact with health systems and interventions and include, for example, stigma, discrimination, racism, sexism, food security/insecurity, housing stability/ instability, and economic inequality. Although the importance of social factors in health is increasingly recognized, there is a persistent need to rigorously model, map, and measure nuanced social dynamics. Greater investment in basic behavioral and social science is needed to further identify, operationalize, measure, and chart causal pathways between core psychological and social factors and HIV outcomes, including health disparities and inequalities.

Further research will lead to better understand and address the interactive nature of social factors, such as intersectional stigma, which is based on multiple aspects of people's identities, social positions, and health status.

With additional resources, NIH will accelerate research in key areas of basic biomedical, behavioral, and social research to advance foundational understanding and develop more focused and effective HIV prevention, treatment, care, cure, and communication strategies.



The COVID-19 pandemic has made evident the critical role of evidence-based science communication in achieving desirable public health outcomes. Yet science communication remains an area of insufficient investment. As new HIV prevention, treatment, and cure strategies are rolled out and scaled up, it is vital that individuals and communities understand how the strategies work and the benefits of implementation. Greater investment in communications science is essential to better understand the nuances of developing and delivering appropriate and effective HIV information to different populations. Equally important is to develop communications strategies in partnership with community and other stakeholders to combat misinformation and address health care mistrust. Effective communications research and training.

The application of basic, behavioral, and social research findings in these areas will collectively improve HIV testing, increase engagement and retention in prevention and care services, and enhance the health and well-being of persons with and at risk for HIV in underserved and marginalized communities.



Co-occurring Conditions

Although ART increases the life expectancy of persons with HIV, there are challenges related to HIV and HIV-associated comorbidities, coinfections, and complications across the lifespan. Clinical conditions co-occur with social conditions that affect people's HIV and associated health outcomes in significant ways that require increased understanding and management.

HIV Across the Lifespan

Much progress has been achieved in preventing perinatal transmission of HIV in the United States, attributed to routine HIV screening of pregnant persons, use of ART for treatment and prophylaxis, avoidance of breastfeeding, and use of elective cesarean delivery when appropriate. With these interventions, rates of HIV transmission during pregnancy, labor, or delivery from mothers infected with HIV have been reduced to less than 2 percent, compared with transmission rates of 25 percent to 30 percent with no interventions. The most recent data from 2018 show that only 65 HIV infections in the United States were attributed to perinatal transmission, a reduction of almost 95 percent from the 1990s.^{22,23}

Limited ART formulations for infants and children make HIV management in these age groups challenging. Questions remain about the impact of HIV and ART exposure in utero, as well as HIV infection and long-term antiretroviral therapy on the growing and developing child. Although early treatment reduces morbidity and mortality from HIV, it is unclear whether very early ART can ameliorate complications of HIV and preserve neurodevelopment, optimal cognitive functioning, and mental health in children with HIV.

In 2019, young people aged 13–24 years represented 21 percent of all new HIV infections in the United States.²⁴ Although improved routine HIV testing has reduced undiagnosed HIV infection in the United States, the largest percentage (44.3) of undiagnosed infection was that among young people. Durable linkage to care, which is associated with improved outcomes, remains an elusive goal for young persons. Regulatory approval of novel treatment strategies in adolescents lags behind approval for adults. Adolescents with perinatally or behaviorally acquired HIV face unique challenges during the transition from pediatric to adult health care settings, including interruptions in HIV care, changing socioeconomic and health insurance status, and stigma and disclosure issues. Cognitive development and mental health issues, medication adherence, and sexual, reproductive, and gender health concerns are paramount in young adults with HIV.

Over half of Americans currently living with HIV in the United States are 50 years or older, and about 10 percent of new infections occur in people age 55 and older.²⁵ This group is expanding with increased use of effective ART among those newly diagnosed with HIV. At the same time, individuals aging with HIV are also more likely to suffer from the effects of accelerated aging, higher rates of neurocognitive and cardiovascular complications, some malignancies, and metabolic and bone disorders, most likely caused by chronic low-level activation of the immune system.²⁶ An increase in the risk of experiencing cardiovascular diseases and increased arterial "age" are some examples of health problems affecting people aging with HIV.

An interdisciplinary approach that includes geroscience²⁷—the study of the intersection between basic aging biology and chronic disease—and the social sciences is required to address the growing health concerns and improve health outcomes in people living and aging with HIV, given that most comorbidities are multifactorial and include lifestyle factors.

Coinfections and Syndemics

At a population level, COVID-19 is threatening gains achieved by 4 decades of HIV/AIDS research.⁸ For example, globally, between 2019 and 2021, people reached by evidence-based HIV prevention services declined by 11 percent overall and by 12 percent for young people; medical male circumcision declined by 27 percent; and HIV testing declined by 22 percent.²⁸ The intersection of two global pandemics is a continuously evolving situation that requires careful analysis of emerging data and creative interventions to mitigate regressive outcomes for people with or at risk of HIV.

With additional resources, NIH will accelerate research to address co-occurring biological, behavioral, and social conditions that contribute to HIV transmission and to suboptimal health outcomes for individuals with HIV across the lifespan.



The full impact of COVID-19 among people with HIV is yet unknown, particularly considering preexisting health inequalities and adverse social determinants of health.²⁹ A recent analysis of data from the NIH-funded U.S. National COVID Cohort Collaborative (N3C) found that people with HIV had higher odds of COVID-19 death than people without HIV; older, male, Black, African American, Hispanic, and Latinx adults with HIV had elevated odds of death; and a lower CD4 cell count was associated with adverse COVID-19 outcomes, whereas viral suppression was associated only with reduced hospitalization.³⁰

Although COVID-19 is an acute crisis, tuberculosis (TB) is a chronic condition that constitutes the most significant cause of mortality for people with HIV globally, particularly in resource-limited countries.³¹ Among people with latent TB infection, those with HIV are more likely than others to develop TB disease, because HIV weakens the immune system and makes it harder for the body to combat the bacteria that causes TB.³² In general, TB in a person with HIV accelerates HIV replication, is harder to diagnose, spreads faster, is more likely to be fatal if left untreated, is more likely to return after being treated, and poses a significant treatment challenge if the person is infected by a drug-resistant TB strain.³³

Sexually transmitted infections (STIs) are significant challenges for people with HIV. Globally, STI coinfection is particularly pronounced. The effects of HIV infection on immunity can increase susceptibility to other STIs, because people whose immune systems are compromised are less likely to mount a defense against sexually transmitted pathogens. Indeed, there is a reciprocal relationship between HIV and herpes (HSV-2), because both infections can facilitate acquisition of the other.³⁴

Additionally, behavioral health issues co-occur with HIV infection and are frequently associated with violence, marginalization, social discrimination, stigma, and other behavioral and psychosocial challenges in syndemic ways. These complex, intersecting, and synergistic conditions need to be better recognized, understood, and addressed to make lasting improvements in the health and well-being of people aging with HIV.



Transformative Tools

Advances in HIV prevention, treatment, co-occurring conditions, and cure can be optimized with greater investment in the development and application of new technologies, methodologies, and implementation approaches.

Technologies

The most highly effective vaccines currently available for COVID-19 were built on a platform—mRNA—originally developed for HIV

vaccine candidates. The success of the mRNA strategy for COVID-19 vaccines has renewed excitement about the feasibility of leveraging the mRNA platform for the development of new vaccine candidates for HIV prevention, and a phase 1 study testing three different HIV vaccine candidates is now underway in the NIH-funded HIV Vaccine Trials Network (HVTN) to build on the earlier studies.³⁵



Concomitant to vaccine-based HIV prevention strategies, antibody-mediated protection using passive immunity is being tested as an alternative way to prevent HIV infection. Several combinations of broadly neutralizing antibodies (bNAb) are predicted to afford high levels of protection for 4–6 months. Several of these bNAb concepts are currently being tested in phase 1 trials.^{36,37,38,39}

The recent development of novel imaging technologies by NIH intramural scientists and others led to a breakthrough in understanding fundamental aspects of HIV-1 structure and viral life cycle within host cells.^{40,41} This has implications for the design of a new class of therapeutics—capsid inhibitors—the first of which, lenacapavir (LEN), is showing promise for people with HIV who have had multidrug resistance, as well as those who are treatment naive.⁴²

Similarly, single-cell imaging technologies are being used to identify and describe the HIV reservoir and to discover mechanisms of viral reactivation from latently infected cells, which has implications for HIV cure strategies. A recently discovered tool for cure research—the bacterial gene editing mechanism, called CRISPR-Cas—was tested to excise viral HIV from the genomic DNA of people with HIV.⁴³ The first clinical trial investigating CRISPR-based gene therapy as a possible means to achieve HIV cure was approved for initiation by the FDA in September 2021.⁴⁴

Emerging approaches for HIV prevention, treatment, and cure alike involve long-acting formulations of antiretroviral drugs administered through injection, vaginal rings, or long-release patches, for example.^{45,46,47} Further development of new formulations and routes of administration will lead to increased options for people and will enhance their ability to exercise choice in their approach to preventing or managing HIV.

Methodologies

The expanding repertoire of effective HIV prevention and treatment modalities increases challenges for ethical reasons to conduct placebo-controlled trials of new methods. Moreover, in populations with relatively low but still meaningful HIV infection rates, ascertaining the efficacy of an HIV prevention method through the usual randomized clinical trial design is unfeasible because of the size of the trial required to detect an effect. The high cost and complex logistics of conducting large-scale randomized trials is becoming prohibitive. These realities underscore the need to invest in the development of innovative methodological approaches for testing promising new interventions.

One method for facilitating next-generation PrEP trials (where using a placebo arm is unethical) is to use HIV recent infection testing algorithms (RITAs), such as the limiting antigen avidity assay plus viral load. This can be used to derive a "counter-factual" incidence estimate using specimens from people with HIV, identified during screening, who are not on treatment and comparing these to on-PrEP incidence.⁴⁸ Further research is essential to ascertain validity and feasibility of this method in different populations.⁴⁹

To enhance feasibility, flexibility, and efficiency in clinical trials of biomedical and behavioral interventions, many researchers are employing adaptive designs (ADs). ADs utilize interim results of the trial to make modifications to the ongoing trial in accordance with predetermined decision rules and without undermining the trial's integrity or validity. The aim is to identify the most effective components of the intervention under study and the most efficient combinations of them and thus to narrow the focus of the intervention to what most likely will work.⁵⁰ Two commonly used ADs are the Multiphase Optimization Strategy (MOST) and the Sequential Multiple Assignment Randomized Trial (SMART). MOST includes a screening, refining, and confirming phase; SMART is an innovative design that identifies the best tailoring variables and decision rules for adapting an intervention.⁵¹

Implementation Approaches

To advance the domestic goals of the NHAS and the EHE initiative and the global targets of the Join United Nations Programme on HIV/AIDS (UNAIDS),⁵² it is imperative to identify effective methods to implement research findings and optimize uptake of the most effective HIV prevention, treatment, and support strategies. To increase rates of sustained viral suppression and improve health outcomes among people with HIV, implementation science research is necessary to bring new findings and strategies into practice in diverse settings and to scale them up within existing systems of health care.

Addressing the special circumstances and needs of different populations, particularly those most disproportionately affected by HIV, requires increased investment in the development, implementation, and scale-up of differentiated HIV prevention, treatment, and cure strategies.

With additional resources, NIH will accelerate research on novel technologies for HIV prevention, treatment, and cure to—

- > Expand the array of options to meet diverse user preferences.
- > Support increased development and testing of innovative methodologies to yield greater efficiencies in the conduct of rigorous clinical trials.
- > Expand research that applies implementation science theories, frameworks, and designs to translate interventions to health practice.
- > Increase research on developing appropriate metrics and methodologies to assess health systems, organizational contexts, and implementation outcomes in diverse settings.



Capacity-strengthening

NIH prioritizes researcher training and development to expand the pool and diversity of the HIV/AIDS research workforce and to help strengthen capacity at historically under-resourced institutions.

Early-Career HIV Investigators

NIH is committed to the development of the next generation of multidisciplinary HIV/AIDS researchers, particularly women and those from underrepresented populations and institutions within

the United States. To expand the pool and diversity of early-career investigators (ECIs), including NIH-defined Early-Stage Investigators (ESIs) and to respond to recommendations from stakeholders, OAR developed an initiative to increase HIV ESI awards by 20 percent in FY 2020 and FY 2021. Additionally, in FY 2021, OAR convened a series of four virtual listening sessions with HIV ECIs to hear directly from them about the challenges and opportunities they face. Following these listening sessions, OAR convened an Expert Panel consultation involving 19 senior HIV investigators and experienced mentors from a variety of academic institutions.

Based on the input from these sessions, OAR is working with the NIH ICOs to implement several actions to develop and support HIV-focused ECI initiatives; identify highly meritorious but unfunded HIV/AIDS research applications from ECIs; continue engagement with ECIs and mentor stakeholders; focus on those ECIs from underrepresented minority groups and under-resourced institutions; and host a symposium to bring together HIV-focused early-career and senior investigators and OAR and NIH program officials.

Expanding Diversity in the HIV/AIDS Research Workforce

NIH supports collaborative initiatives to strengthen research capacity among underrepresented and under-resourced institutions to facilitate greater diversity in the HIV/AIDS research workforce at all career stages. For example, in FY 2020, OAR co-funded supplements with the NIH Sexual & Gender Minority Research Office (SGMRO) for four HIV-related extramural research projects and provided supplements to the Research Centers in Minority Institutions (RCMI) Program of the National Institute on Minority Health and Health Disparities (NIMHD) to support research laboratory renovations for

With additional resources, NIH will accelerate the development and expansion of novel programs for training, support, and capacitystrengthening of underrepresented individuals and under-resourced institutions to enhance diversity in the HIV workforce.





HIV-related research activities at two RCMI institutions. In FY 2021, OAR collaborated with NIMHD and the National Institute of General Medical Sciences (NIGMS) to support an increased number of physical infrastructure projects at RCMI, Institutional Development Award (IDeA), and Native American Research Centers for Health (NARCH) institutions.

Conclusion

Resources made available through this FY 2023 Professional Judgment Budget estimate will allow NIH to expand HIV science in focused priority areas of research and ensure that evidence-based strategies are central components of national HIV initiatives. These additional funds will accelerate the pursuit of key advances in—

- > Basic biomedical, behavioral, and social research to advance foundational understanding and develop effective HIV prevention, treatment, care, cure, and communication strategies
- Research to address co-occurring biological, behavioral, and social conditions that contribute to HIV transmission, disparities, and suboptimal health outcomes for individuals with HIV across the lifespan
- > Novel technologies for HIV prevention, treatment, and cure, as well as metrics and methodologies to assess health systems, organizational contexts, and implementation outcomes in real-world settings
- > Application of implementation science theories, frameworks, and innovative designs to translate successful interventions to health practice
- > New programs for expanding training, support, and capacity-strengthening of underrepresented individuals and under-resourced institutions to enhance diversity in the HIV workforce

Continued investment is needed to sustain the momentum that has changed the lives of people with HIV over the last 40 years. An expanded, integrated strategic approach will lead to innovative research efforts and new discoveries, paving the way to halting new HIV transmissions and improving the lives of persons with and affected by HIV.

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Acronyms/Abbreviations

AD	Adaptive design
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral treatment
bNAb	Broadly neutralizing antibody
CCC	HIV-associated comorbidities, coinfections, and complications
COVID-19	Coronavirus disease 2019
CRISPR	Clustered regularly interspaced short palindromic repeats
ECI	Early-career investigator
EHE	Ending the HIV Epidemic in the U.S. initiative
ESI	Early-stage investigator
FDA	U.S. Food and Drug Administration
FY	Fiscal Year
HIV	Human immunodeficiency virus
HSV-2	Herpes simplex virus type 2
HVTN	HIV Vaccine Trials Network
ICOs	NIH Institutes, Centers, and Offices
IDeA	Institutional Development Award
LEN	Lenacapavir
MOST	Multiphase Optimization Strategy
mRNA	Messenger RNA
N3C	National COVID Cohort Collaborative
NARCH	Native American Research Centers for Health
NHAS	National HIV/AIDS Strategy
NIH	National Institutes of Health

NIGMS	National Institute of General Medical Sciences
NIMHD	National Institute on Minority Health and Health Disparities
OAR	NIH Office of AIDS Research
PrEP	Pre-exposure prophylaxis
RCMI	Research Centers in Minority Institutions
RITA	Recent infection testing algorithm
saRNA	Self-amplifying RNA
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGMRO	NIH Sexual & Gender Minority Research Office
SMART	Sequential Multiple Assignment Randomized Trial
STI	Sexually transmitted infection
ТВ	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS

