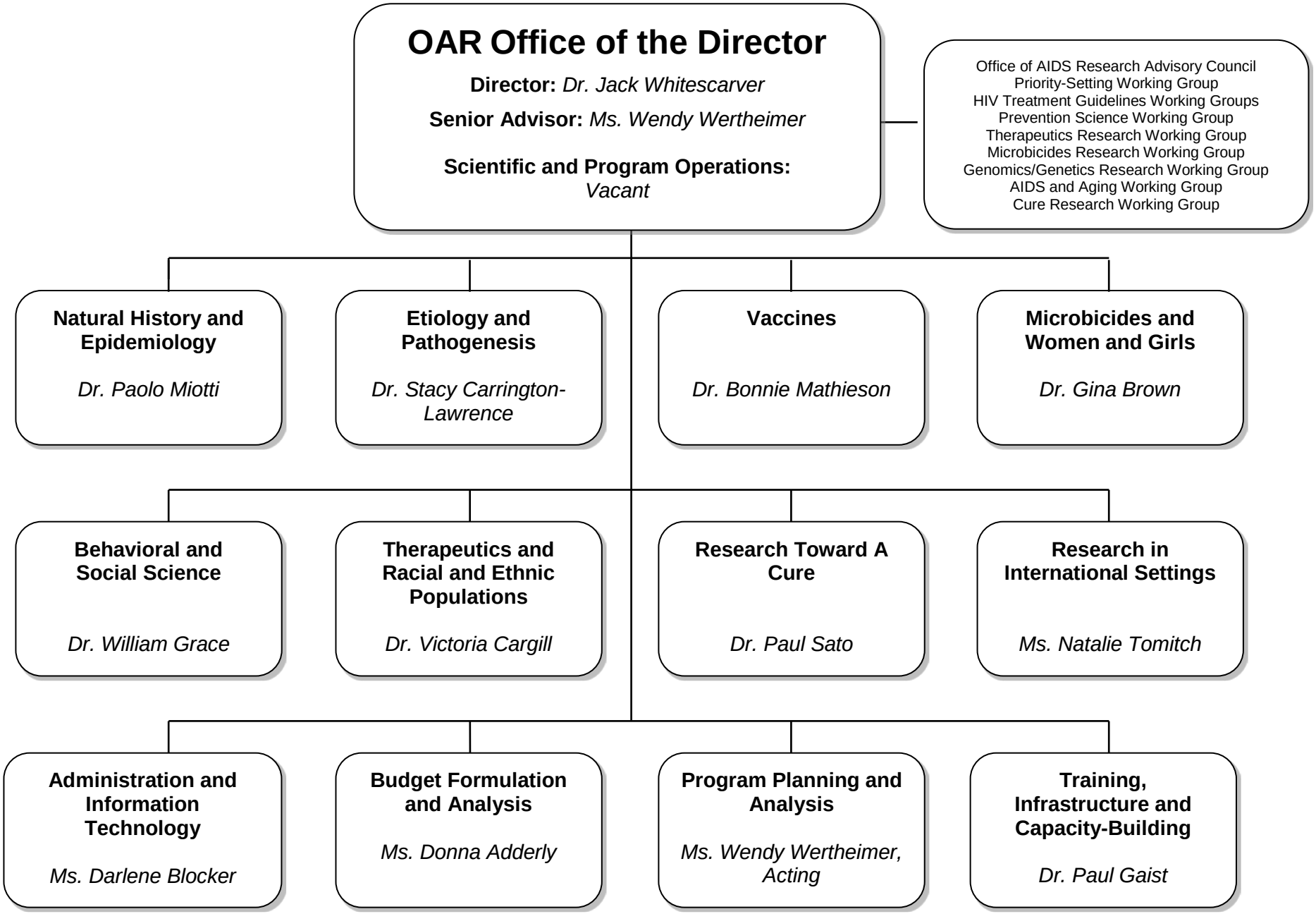
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Trans-NIH AIDS Research Budget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Scientific and Program Operations:
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Office of AIDS Research Advisory Council
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HIV Treatment Guidelines Working Groups
Prevention Science Working Group
Therapeutics Research Working Group
Microbicides Research Working Group
Genomics/Genetics Research Working Group
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Cure Research Working Group
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NATIONAL INSTITUTES OF HEALTH
Office of AIDS Research
Budget Authority by Institute and Center
(Dollars in Thousands)

Institute / Center	FY 2014 Actual	FY 2015 Enacted	FY 2016 President's Budget	FY 2016 +/- FY 2015
NCI	$269,212	$269,660	$281,130	$11,470
NHLBI	64,044	64,974	66,552	1,578
NIDCR	18,414	17,465	18,002	537
NIDDK	29,952	30,031	31,262	1,231
NINDS	45,345	45,465	45,619	154
NIAID	1,563,878	1,586,804	1,648,753	61,949
NIGMS	64,096	64,963	67,147	2,184
NICHD	140,245	142,016	147,069	5,053
NEI	1,740	1,360	925	-435
NIEHS	5,165	5,179	5,179	--
NIA	5,451	5,465	5,700	235
NIAMS	4,766	4,779	4,999	220
NIDCD	1,816	1,821	1,847	26
NIMH	157,005	156,687	163,521	6,834
NIDA	300,714	298,862	302,211	3,349
NIAAA	27,464	27,537	29,189	1,652
NINR	12,234	12,266	12,757	491
NHGRI	6,900	6,380	6,411	31
NIBIB	1,220	713	395	-318
NIMHD	19,787	21,839	23,367	1,528
NCCIH	1,558	975	777	-198
NCATS	66,122	64,287	64,827	540
FIC	23,458	23,520	24,909	1,389
NLM	7,917	7,937	8,437	500
OD				
OAR	61,923	61,923	61,923	--
ORIP	77,153	77,153	77,153	--
Subtotal, OD	139,076	139,076	139,076	--
TOTAL, NIH	**$2,977,579**	**$3,000,061**	**$3,100,061**	**$100,000**

NATIONAL INSTITUTES OF HEALTH
Office of AIDS Research
Budget Mechanism - AIDS [1]

(Dollars in Thousands)

MECHANISM	FY 2014 Actual		FY 2015 Enacted		FY 2016 President's Budget		FY 2016 +/- FY 2015	
	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting	1,567	$932,970	1,654	$1,289,448	1,637	$1,287,895	-17	-$1,553
Administrative Supplements	*(130)*	29,359	*(61)*	21,726	*(60)*	21,686	*(-1)*	-40
Competing	703	628,085	662	338,415	779	416,298	117	77,883
Subtotal, RPGs	2,270	$1,590,414	2,316	$1,649,589	2,416	$1,725,879	100	$76,290
SBIR/STTR	67	35,217	64	36,256	65	36,015	1	-241
Research Project Grants	2,337	$1,625,631	2,380	$1,685,845	2,481	$1,761,894	101	$76,049
Research Centers:								
Specialized/Comprehensive	61	$142,705	58	$141,708	57	$133,691	-1	-$8,017
Clinical Research	1	61,746	1	59,911	1	60,451	--	540
Biotechnology	0	491	0	246	0	246	--	--
Comparative Medicine	26	58,764	27	59,266	26	58,566	-1	-700
Research Centers in Minority Institutions	13	9,018	9	6,350	7	5,320	-2	-1,030
Research Centers	101	$272,724	95	$267,481	91	$258,274	-4	-$9,207
Other Research:								
Research Careers	236	$40,029	236	$38,614	240	$39,403	4	$789
Cancer Education	0	0	0	0	0	0	--	--
Cooperative Clinical Research	8	14,023	8	14,022	8	14,022	--	--
Biomedical Research Support	0	1,884	0	1,644	0	1,644	--	--
Minority Biomedical Research Support	1	337	1	336	1	336	--	--
Other	157	61,124	159	61,092	163	61,529	4	437
Other Research	402	$117,397	404	$115,708	412	$116,934	8	$1,226
Total Research Grants	2,840	$2,015,752	2,879	$2,069,034	2,984	$2,137,102	105	$68,068
Ruth L. Kirschstein Training Awards:	FTTPs		FTTPs		FTTPs			
Individual Awards	98	$4,637	99	$4,309	97	$4,319	-2	$10
Institutional Awards	652	33,404	658	34,023	654	34,095	-4	72
Total Research Training	750	$38,041	757	$38,332	751	$38,414	-6	$82
Research & Develop. Contracts	100	$410,255	102	$382,076	102	$402,428	0	$20,352
(SBIR/STTR) (non-add)	*(2)*	*(537)*	*(4)*	*(1,287)*	*(4)*	*(1,200)*	*0*	*(-87)*
Intramural Research		$336,128		$332,166		$341,625		$9,459
Res. Management and Support		115,480		116,530		118,569		2,039
Res. Management & Support (SBIR Admin) (non-add)								
Office of the Director - Appropriation		*139,076*		*139,076*		*139,076*		--
Office of the Director - Other [2]		61,923		61,923		61,923		--
ORIP (non-add) [2]		*77,153*		*77,153*		*77,153*		--
Total, NIH Discretionary B.A.		**$2,977,579**		**$3,000,061**		**$3,100,061**		**$100,000**

[1] All items in italics and brackets are non-add entries. FY 2014 and FY 2015 levels are shown on a comparable basis to FY 2016.

[2] Number of grants and dollars for the ORIP components of OD are distributed by mechanism and are noted here as a non-add.

NATIONAL INSTITUTES OF HEALTH
Office of AIDS Research
Budget Authority by Activity
(Dollars in Thousands)

Area of Emphasis	FY 2012 Actual	FY 2013 Actual	FY 2014 Actual	FY 2015 Enacted	FY 2016 President's Budget	FY 2016 +/- FY 2015
Vaccines	$556,613	$518,170	$532,671	$537,402	$567,947	$30,545
HIV Microbicides	129,919	111,240	107,843	108,349	113,072	4,723
Behavioral and Social Science	420,084	397,377	411,723	414,873	423,038	8,165
Etiology and Pathogenesis	668,244	625,027	666,569	670,527	698,310	27,783
Therapeutics						
Therapeutics as Prevention	*56,561*	*69,375*	*75,638*	*73,696*	*74,472*	*776*
Drug Discovery, Development, and Treatment	*650,059*	*632,123*	*660,194*	*671,857*	*685,653*	*13,796*
Total, Therapeutics	706,620	701,498	735,832	745,553	760,125	14,572
Natural History and Epidemiology	257,973	243,454	228,830	230,437	236,868	6,431
Training, Infrastructure, and Capacity Building	280,775	261,921	259,866	257,591	264,978	7,387
Information Dissemination	54,567	39,178	34,245	35,329	35,723	394
Total	$3,074,795	$2,897,865	$2,977,579	$3,000,061	$3,100,061	$100,000

The Global AIDS Epidemic

UNAIDS 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.
- there were about **2.1 million** new infections 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 (ARV) 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 half (50%) of all adults living with HIV worldwide. HIV is the leading cause of death among women of reproductive age.
- 33% of new infections were among young people, ages 15-24
- **3.2 million** children were living with HIV; there were 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 are 15-30%, and increase to 45% with breastfeeding; 33% of pregnant women in low and middle-income countries do not receive ARV therapy to prevent mother-to child HIV transmission

The AIDS Epidemic in the United States

The Centers for Disease Control (CDC) reports that in the U.S.:

- more than **1.2 million** people are living with HIV
- over **650,000** people have died
- new infections have remained at about **50,000** per year for more than a decade
- while many people with HIV are diagnosed (86%), fewer are engaged in care (40%) and are prescribed ARV treatment (37%)
- only **30%** of individuals living with HIV are virally suppressed (the point at which the virus is under control and a person can remain healthy and reduce the risk of transmission) and viral suppression is even lower among African Americans (21%) and young people ages 25-34 (15%)
- therefore, **70% do not have their virus under control.**

Justification of Budget Request

Office of AIDS Research
Trans-NIH AIDS Research Budget Justification
(see also: OAR section in Office of the Director/DPCPSI)

Budget Authority (BA):

FY 2014 Actual	FY 2015 Enacted	FY 2016 President's Budget	FY 2016+/- FY 2015
$2,977,579,000	$3,000,061,000	$3,100,061,000	$100,000,000

Director's Overview

Groundbreaking Accomplishments but Monumental Challenges: The human and economic toll of the AIDS pandemic is profound. It requires a unique response that is complex, comprehensive, multi-disciplinary, and global. In the three decades since the first cases of AIDS were reported, NIH has been the global leader in research to understand, prevent, diagnose, and treat HIV and its many related conditions. NIH has established a comprehensive and coordinated AIDS research program that has demonstrated unprecedented progress against this worldwide epidemic. Despite this progress, the HIV/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. Although much has been accomplished, the investment in HIV-related research is just beginning to reap rewards, opening new possibilities and scientific opportunities to make progress against AIDS and its associated illnesses and consequences.

Coordinated Trans-NIH AIDS Research Program: The NIH AIDS research program that produced these critical accomplishments is coordinated and managed by the Office of AIDS Research (OAR), which functions as an "institute without walls" with responsibility for AIDS-related research supported by every NIH Institute and Center (IC). It is essential to point out that because AIDS affects virtually every organ system, with a myriad of HIV-associated infections, malignancies, co-morbidities and clinical complications, NIH AIDS research supports a vast portfolio that also includes research on 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. OAR has established comprehensive trans-NIH planning, budgeting, and portfolio analysis processes to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively. OAR also identifies specific funding for 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 jump-start or pilot program areas; facilitates international AIDS research and training; and sponsors scientific agenda setting workshops to identify new cutting-edge initiatives.

Annual Trans-NIH Strategic Plan and Budget: 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 and strategies. This comprehensive and unique annual process involves scientists from across NIH and other Federal agencies, non-government experts, and constituency groups. OAR also is mandated to develop an annual trans-NIH AIDS research budget explicitly tied to the objectives of the Strategic Plan. Thus, this budget request is informed by the FY 2016 Trans-NIH Plan for HIV-Related Research (Strategic Plan). OAR's AIDS research allocation to each IC is not based on a formula, but on the scientific priorities and objectives of the Strategic Plan, taking into account the current scientific opportunities and priorities, the evolving clinical profile of the epidemic, and the IC's capacity to absorb and expend resources for the most meritorious science. This process reduces redundancy, promotes harmonization, and assures cross-Institute collaboration to conduct and support research in domestic and international settings.

Priority-Setting Review: The OAR Advisory Council has also reaffirmed the key scientific priorities. Over the past year, OAR conducted a priority-setting portfolio review of the entire AIDS research program to re-examine and affirm the highest priorities for NIH AIDS research. OAR will continue to allocate and redirect resources across the ICs and across the key areas of science to address these priorities.

Challenges and Opportunities for FY 2016: The key scientific priorities for NIH AIDS research that shape the Trans-NIH AIDS research budget request are:

Translating Discovery into Health

- **Prevention Research**: NIH will support 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 antiretroviral therapy as prevention.
- **Treatment:** NIH will support HIV treatment 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 co-morbidities; and more likely to achieve eradication of infection. NIH will also 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.
- **Research Toward a Cure:** NIH will support research related to the potential for a cure or lifelong remission of HIV infection, including studies on viral persistence, latency, reactivation, and eradication.
- **Co-Infections, Co-Morbidities and Complications:** NIH will support research on the treatment and prevention of HIV- related co-infections, malignancies, and neurological, cardiovascular, and metabolic complications.
- **Behavioral and Social Science Research:** NIH will support research on understanding factors that fuel or mitigate HIV epidemics; the role of stigma; and adherence to treatment or prevention strategies, particularly to address the HIV Care Continuum.

***Preparing a Diverse and Talented Biomedical Research Workforce*:** NIH will train the next generation of AIDS researchers around the world to foster collaboration, innovation, and transformative research.

Overall Budget Policy:

To address these critical AIDS research priorities, the FY 2016 President's Budget estimate for the trans-NIH AIDS research program is $3,100.061 million, an increase of $100.000 million or 3.3 percent above the FY 2015 Enacted level. The OAR is authorized to allocate all dollars associated with this area of research across the NIH. Therefore, the total for AIDS research includes both extramural and intramural research (including research management support, management fund, and service and supply fund); buildings and facilities; and training and evaluation. The total also includes basic, clinical, behavioral, social science, and translational research on HIV/AIDS and the many HIV-associated malignancies, co-infections, co-morbidities, and complications, including TB, hepatitis C, and HIV-associated cancers. Thus, the total for AIDS-related research is not comparable to spending reported for other individual diseases. This request reflects the shifting of funds across ICs to address new and exciting scientific opportunities in AIDS research identified through OAR's unique trans-NIH strategic planning, priority-setting, portfolio analysis, and budget processes and to address the evolving clinical profile of the epidemic. This request provides increased funding to support high priority basic research (etiology and pathogenesis), the underlying foundation for all HIV prevention and treatment research, as well as research to better understand disease progression and HIV-related co-morbidities. Increased funds are provided for the key priority of prevention research, particularly new opportunities in the development of vaccines. In FY 2015, OAR launched a three-year (FY 2015-2017) commitment to provide $100 million in redirected funds to research towards a cure. OAR provided the initial investment of $15 million in additional cure research in FY 2015, bringing the total to $127.3 million. This FY 2016 request includes a $21.8 million increase to support the second year of the commitment, which will total $149.1 million in FY 2016 (see page 13 for details) . These increased funds are provided for basic research, treatment research, and novel therapeutic vaccine research. Increased funds are also provided for research on new, long-acting, more effective and less toxic ARV therapies for both treatment and prevention.

Program Descriptions and Accomplishments

Vaccines: The best long-term hope for controlling the AIDS pandemic is the development of safe, effective, and affordable AIDS vaccines that may be used in combination with other prevention strategies. 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, 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 II vaccine clinical studies present new scientific opportunities for the development of improved HIV vaccine candidates.

Budget Policy:
The FY 2016 President's Budget request for Vaccine research is $567.947 million, an increase of $30.545 million or 5.7 percent above the FY 2015 Enacted level. Innovative basic HIV vaccine research studies will be supported to inform the development of new vaccine concepts that might induce higher levels of protective antibodies and prevent HIV infection more efficiently than vaccines already tested. In FY 2016, NIH will fund additional development of improved animal models including new models for vaccine challenge studies in non-human primates to test vaccine concepts and to aid informed testing of HIV vaccine candidates in clinical trials. NIH will provide support for new initiatives to integrate systems biology with HIV vaccine discovery, and will fund additional research to develop new tests to measure immune responses to the HIV vaccine candidates that will more closely predict outcomes of parallel preclinical animal and human clinical studies. Resources will be directed toward the development and testing of improved vaccine candidates in additional clinical studies, both in the U.S. and abroad, building on the early protection observed in the previous Phase III vaccine trial in Thailand. Increased support will be provided for clinical trials that evaluate the ability of monoclonal antibodies from HIV-infected individuals. These trials have been initiated in participants in the U.S. and will enable us to understand how they will be able to prevent HIV infection, delay disease progression or eliminate HIV-infected cells. The increases provided to vaccine research reflect OAR's redirections of funds from other scientific areas to support critical research opportunities in this area.

HIV Microbicides: A safe and effective microbicide will be an important asset to the HIV prevention tool kit. Microbicides are products, including antiretroviral (ARV) drugs and other agents, that could be applied topically or injected to prevent acquisition of HIV and other sexually transmitted infections. Microbicides could be used alone or in combination with other strategies. NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, formulation, preclinical testing, and clinical evaluation of microbicide candidates. NIH supports basic science research aimed at understanding how HIV crosses mucosal membranes and infects cells. In addition, 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 sexually transmitted infections (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.

Budget Policy:
The FY 2016 President's Budget request for Microbicides research is $113.072 million, an increase of $4.723 million or 4.4 percent above the FY 2015 Enacted level for this area of prevention research. In FY 2016, 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. Key ongoing activities include support for the NIH-funded Microbicide Trials Network (MTN); the integration of behavioral and social sciences research with clinical studies to better understand issues of adherence; and the necessary infrastructure to conduct basic, behavioral, social sciences and clinical microbicides research. Research activities will utilize this infrastructure to build on recent scientific advances and develop innovative, novel, and high risk-high reward approaches for the discovery, development, formulation, and testing of microbicide candidates and delivery systems and the formulation of biomarkers to assess product adherence. Research also will focus on the development and testing of multi-purpose prevention technologies (MPTs) that prevent HIV and other sexually transmitted infections or HIV and pregnancy; and on the continued study of animal and tissue models designed to enhance understanding of the mechanisms of HIV infection and assist safety and efficacy evaluations of candidate microbicide products. NIH will support research needed for the development of criteria for the selection of candidate microbicides to be advanced through the different phases of preclinical and clinical studies including clinical safety and effectiveness studies and research on ethics, adherence, and other behavioral and social science issues that can impact clinical trials and microbicide use. Through a number of trans-governmental working groups and non-governmental expert consultations, OAR will continue to foster coordination and collaboration in innovative microbicide research leading to the development and testing of novel potential candidates that can prevent HIV transmission and acquisition.

Behavioral and Social Science: As studies continue to define a role for the use of ARV medications for HIV prevention, NIH is supporting research to understand how these drugs can best be used for prevention in specific populations and social contexts. 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. NIH is supporting research to address factors associated with the HIV Care Continuum, and specifically on HIV care outcomes. The HIV Care Continuum, sometimes called the HIV treatment cascade, is a model used to identify issues and opportunities related to improving the proportion of HIV-infected individuals who are engaged at each stage of HIV care -- from diagnosis to linkage to care, retention in care, receipt of appropriate ARV treatment, and achieving viral suppression. Investigations are not only focused on individual-level variables, but 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. NIH also 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. NIH will also continue to foster the integration of biomedical and behavioral strategies in clinical investigations.

Budget Policy:
The FY 2016 President's Budget request for Behavioral and Social Science is $423.038 million, an increase of $8.165 million or 2.0 percent above the FY 2015 Enacted level. NIH will continue to shift its investments within the area of behavioral and social sciences to keep pace with the increasing integration of biomedical and behavioral perspectives, the success of antiretroviral medications in both prevention and treatment, and the key role of adherence to this success. Increased attention will be given to research to improve the implementation of new prevention and therapeutic strategies in specific populations and social contexts. Research to address issues of stigma and to improve access to prevention and treatment resources will be supported, and a strong emphasis on basic science to understand both the social and biomedical (e.g., neurophysiologic and genomic) factors related to risk behaviors. NIH will support initiatives to better understand the multiple factors related to adherence, utilizing novel ways to ensure that patients take their medications and use prevention strategies appropriately.

Etiology and Pathogenesis (Basic Science): 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, diagnostic methods, and tools for monitoring disease progression and the safety and effectiveness of antiviral therapies. Ground-breaking 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; determine the role of immune dysfunction and chronic inflammation in HIV pathogenesis; and further the understanding of the development of HIV-associated co-morbidities, such as cardiovascular, neurological, and other clinical complications, malignancies, and co-infections. Research is also needed to examine the host microbiome as well as the genetic determinants associated with HIV susceptibility, disease progression, and treatment response. 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. 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.

Budget Policy:
The FY 2016 President's Budget request for the basic research area of Etiology and Pathogenesis is $698.310 million, an increase of $27.783 million or 4.1 percent above the FY 2015 Enacted level. Studies related to the development of microbicides and vaccines as well as research

toward a cure have revealed gaps in knowledge and understanding of HIV etiology and pathogenesis, particularly with regard to host immune responses, how HIV interacts with and crosses host target surfaces, the interplay between the host microbiome and HIV, and the establishment and maintenance of latent viral reservoirs in the body (HIV persistence). NIH will provide increased resources for research on the biology of HIV transmission and pathogenesis studies including research on HIV-associated immune system dysfunction and chronic inflammation. NIH will support studies of clinical complications, such as HIV-associated co-infections, malignancies, premature aging, cardiovascular disease, neurological and metabolic disorders. Funds will be provided for research to better understand the differences in HIV transmission, treatment, and progression in women compared to men as well as the unique clinical manifestations of HIV disease in women. A key component of the NIH HIV cure research initiative will focus on studies on viral persistence, latency, and reactivation.

Program Portrait: The NIH HIV Cure Research Initiative

FY 2015 Level:	$ 127.3 million
FY 2016 Level:	$ 149.1 million
Change:	$+ 21.8 million

Research related to the potential for a cure or lifelong remission of HIV infection is a key NIH research priority, which involves research across a number of scientific areas. Although combination ARV therapy has 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 NIH because of the continued risks for HIV- associated clinical complications even with ARV use, the side effects of the drugs, and because the need for lifelong ARV therapy 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 difficult goal to achieve. Yet the same research has demonstrated that prolonged and sustained HIV remission with concomitant absence of chronic immune activation may be possible off ARV 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, are also especially needed. Continued work is vital on therapeutic interventions for inducing sustained viral remission. 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 in the central nervous system. NIH will also continue to support preclinical and clinical trials of innovative cure strategies including those incorporating therapeutic vaccines and anti-HIV monoclonal antibodies. More must be learned about the nature of long-lived tissue and cellular reservoirs of latent HIV and the factors affecting HIV rebound following cessation of antiretroviral therapy. Research into new mathematical, cellular, and animal models is also supported under this initiative.

Therapeutics

Drug Discovery, Development, and Treatment: Antiretroviral (ARV) treatment 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 ARV drugs. With the expansion of the classes of ARV available, the regimens required to provide viral suppression have been greatly simplified. ARV treatment has not only delayed the progression of HIV disease to AIDS, it has been increasingly effective at prolonged viral

suppression and delayed development of viral resistance. The addition of integrase inhibitors to the ARV arsenal has enhanced treatment options for the treatment experienced, and novel options for greater virologic control for the treatment naïve. 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, Hepatitis B and C, metabolic dysregulation due to HIV infection and its treatment, as well as AIDS- and non-AIDS defining cancers. The development of the directly acting agents has also significantly changed the impact of Hepatitis C, with more effective agents that can achieve a sustained virologic response in over 90 percent of treated individuals. Nevertheless, the impact of HIV on the reservoirs beyond the reach of antiretrovirals and the progression of renal and hepatic disease unresponsive to treatment remains a significant source of morbidity and mortality for those living with HIV infection, especially those who are from marginalized segments of the population with limited access to care. NIH supports a comprehensive therapeutics research program to design, develop, and test drugs and drug regimens. Under development are new combinations of drugs and sustained release formulations and delivery systems to maintain an undetectable viral load, to overcome drug resistance and treatment failure, and to prevent and treat HIV-associated co-infections, co-morbidities, and other complications. The program supports the HIV cure research initiative with a focus on developing drugs and cell- and gene-based strategies that can target and eradicate persistent viral reservoirs in various cells, tissues, and organ systems, including the central nervous system and brain. This program also is supporting pre-clinical trials of innovative strategies to eliminate viral reservoirs including testing therapeutic anti-HIV monoclonal antibodies with and without antiretroviral drugs.

Improved Therapies for Long-Term Survival

NIH researchers are working to:

- Develop innovative therapies and novel cell-, gene-, and immune-based approaches to control and eradicate HIV infection;
- Develop new formulations, including long-acting therapies;
- Identify new drug targets based on the structure of HIV/host complexes;
- Delineate the interaction of aging and AIDS, including neurological, cardiovascular, and metabolic complications, as well as issues of frailty;
- Discover and develop improved therapies for AIDS-defining and non-AIDS-defining malignancies; and
- Discover the next generation of drugs that may be used in potential "therapeutics as prevention" strategies.

***Therapeutics 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 that 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, helping to establish the foundation for the clinical guidance for the widespread use of PrEP. 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, the use of ARV to prevent infection after HIV exposure, including in a healthcare 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.

Budget Policy:
The FY 2016 President's Budget request for Therapeutics research is $760.125 million, an increase of $14.572 million or 2.0 percent above the FY 2015 Enacted level. Funds will be provided to support high priority research on treatment and prevention of HIV-associated co-infections and co-morbidities; and basic research studies targeting and eradicating HIV reservoirs. Resources will be directed to support: studies of the comparative immunology and molecular oncology of HIV-associated lymphomas; research on AIDS- and non-AIDS defining cancers, especially among older persons with HIV infection; delineating the role of immune activation and residual inflammation and microbial translocation in chronic HIV infection; research on the interaction of aging and neuro-AIDS; development of new strategies to test and treat patients with HIV-related co-infections, including Hepatitis C virus and tuberculosis; conducting clinical studies on cardiovascular and other metabolic complications of HIV disease and ART; treatment of aging HIV-infected individuals to prevent transmission and reduce HIV-associated morbidity and mortality; identifying new drug targets based on the structure of HIV/host complexes; identifying neurobehavioral and neurocognitive factors that result from HIV infection or are modified by HIV infection; and support for strategies to increase HIV testing and linkage to care in adolescent populations. Within the NIH HIV Cure initiative, funds will be provided for expansion of programs targeting innovative approaches to develop and evaluate novel approaches to control and eradicate HIV infection that may lead to a cure; identifying innovative approaches to quantify the latent HIV reservoirs; and novel strategies for targeting the central nervous system viral reservoir without inducing reactivation. Funds also will support research on the discovery and testing of new combinations of ARVs and sustained release formulations and delivery systems that may be used in potential new strategies for treatment and prevention that support adherence, minimize side effects, and maintain viral suppression.

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 co-morbidities and helping to differentiate effects related to long-term ARV treatment from those related to HIV disease and chronic co-

morbidities. As the AIDS epidemic continues to evolve, there is a crucial need for carefully designed epidemiologic studies in domestic and international settings. 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 co-infections, malignancies, 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; between industrialized and resource-constrained nations; between men and women; and health disparities based on sexual identity). Ongoing observational studies are adding focus on at-risk individuals from the rural South in the United States as well as individuals over the age of 50. Research on HIV-related health disparities and their impact on treatment access and effectiveness, as well as HIV prevention, will continue to be an NIH AIDS research priority.

Budget Policy:
The FY 2016 President's Budget request for Natural History and Epidemiology is $236.868 million, an increase of $6.431 million or 2.8 percent over the FY 2015 Enacted level.
NIH will continue to use existing networks and research cohorts to support high-priority epidemiology studies of populations most at risk, including men who have sex with men (MSM), especially MSM of color; women; adolescents; and individuals over fifty years of age who are aging with HIV. Population studies on the long-term effects of HIV disease and of its treatment are critically important at the current stage of the HIV epidemic as are studies of non-communicable disease co-morbidities that have become more commonly diagnosed in HIV-infected people under HIV treatment. Epidemiologic research also will include the development of novel trans-disciplinary methods to examine the treatment and prevention cascades through integration of data from electronic medical records, observational studies, clinical trials and simulation, mathematical modeling, and molecular epidemiology. Resources will be provided for studies of HIV implementation science, including those that advance new methodologies and studies that maximize program effectiveness by addressing organizational and system-level barriers to the scale-up of prevention and treatment interventions. Studies also will be supported to evaluate the economic impact and cost-effectiveness of various intervention strategies in different regions and circumstances.

Training, Infrastructure, and Capacity Building: NIH supports the training of domestic and international biomedical and behavioral HIV researchers. 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 global expansion of the NIH-funded HIV research has necessitated the development of research training, and infrastructure and capacity building efforts in many resource-limited settings throughout the world. The 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 NIH provides to strengthen the conduct of AIDS-related research, both domestically and internationally.

Budget Policy:
The FY 2016 President's Budget estimate for Training, Infrastructure, and Capacity Building is $264.978 million, an increase of $7.387 million or 2.9 percent above the FY 2015 Enacted level. NIH will continue to support training programs and infrastructure development for both U.S.-based and international researchers to build the critical capacity to conduct AIDS research in the United States and in developing countries, including capacity for ongoing efforts to increase the supply of non-human primates and develop other animal models for AIDS research. NIH will support efforts to ensure an adequate number of trained intramural AIDS researchers through the AIDS Research Loan Repayment Program and the Intramural AIDS Research Fellowship program.

Information Dissemination: 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 to 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 men who have sex with men. 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.

Budget Policy:
The FY 2016 President's Budget estimate for Information Dissemination is $35.723 million, an increase of $0.394 million or 1.1 percent above the FY 2015 Enacted level. As the number and complexity of clinical studies increases, 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. Funding also will be provided to ensure that clinical trial information and critical federal guidelines on the use of antiretroviral therapy, as well as guidelines for the management of HIV complications for adults and children, are updated regularly and disseminated widely to healthcare providers and patients through the AIDS*info* website (www.aidsinfo.nih.gov).

Global Impact of NIH AIDS Research: Research to address the global pandemic is essential. Since the early days of the epidemic, 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 healthcare 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.

AIDS Research Conducted in International Settings

(Dollars in Millions)

FY 2014 Actual	FY 2015 Enacted	FY 2016 PB
$453.577	$ 451.199	$462.240

Benefits of AIDS Research to Other Areas: The NIH investment in AIDS research has resulted in critical scientific accomplishments that benefit not only the 35 million HIV-infected individuals around the world, but has also contributed knowledge to the prevention, diagnosis, and treatment of many other diseases and conditions. AIDS research deepens the overall 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 opportunistic infections, co-morbidities, cancers, and other complications).

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 and dementia. AIDS immunology and biology research has informed the understanding of inflammation and 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 fostered significant improvements in drug design and delivery technologies that can improve adherence; and 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 opportunistic infections also now benefit patients undergoing cancer chemotherapy and the more than 28,000 Americans who receive an organ transplant each year. AIDS research also has advanced understanding of the relationship between viruses and cancer. New investments in AIDS research will continue to fuel biomedical advances and breakthroughs that will have profound benefits far beyond the AIDS pandemic.

Conclusion: Despite the groundbreaking scientific advances that have resulted from NIH's investment in AIDS research, many serious challenges lie ahead. There is little doubt that the AIDS pandemic will continue to impact virtually every nation in the world for decades to come. In light of this reality, the United States national commitment to AIDS research remains strong. NIH will continue to build on this important moment in science and to support critical research to find new tools to turn the tide in the fight against this global epidemic so that we can all once again live in a world without AIDS.