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The Role of NIH Research in the Implementation of the PEPFAR Mission

Statement of

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Mr. Chairman and members of the Committee, thank you for the opportunity to discuss the critical role of research supported by the National Institutes of Health (NIH), part of the Department of Health and Human Services (HHS), in advancing the mission of the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Health Initiative (GHI). I am the Director of the National Institute of Allergy and Infectious Diseases (NIAID), the component of the NIH that conducts and supports a substantial proportion of the research on the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). NIH is devoted to better understanding HIV and how it causes disease; developing new and more effective treatments for people with HIV/AIDS; discovering new tools to prevent HIV infection, such as a preventive vaccine; and continuing the ongoing search for a cure for HIV disease.

Twenty-nine years ago, a handful of cases of what is now known as AIDS were first identified here in the United States.[1,2] Since that time, an estimated 597,499 people in the United States have lost their lives to AIDS.[3] More than 56,000 individuals in the United States become infected with HIV each year, and more than 1.1 million Americans currently are living with HIV, according to estimates

[1] Centers for Disease Control and Prevention (CDC). Pneumocystis pneumonia: Los Angeles. *MMWR*. 1981;30(21):250-252.
[2] Centers for Disease Control and Prevention (CDC). Kaposi's Sarcoma and Pneumocystis pneumonia among Homosexual Men: New York City and California. *MMWR*. 1981;30(25): 305-308.
[3] Centers for Disease Control and Prevention (CDC). *HIV Surveillance Report, 2008*; vol 20. June, 2010. Available at http://www.cdc.gov/hiv/surveillance/resources/reports/2008report/.

from the Centers for Disease Control and Prevention (CDC).[4] Globally, the challenges are even greater. Approximately 33.4 million people worldwide are currently living with HIV, and in 2008 alone an estimated 2.7 million people became newly infected with HIV; 2 million died from HIV disease.[5] The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that approximately 60 percent of HIV-infected people worldwide do not know their infection status, precluding them from seeking care and significantly increasing the risk that they will unwittingly transmit the virus to someone else.[6]

The public health response to the HIV/AIDS pandemic involves a variety of approaches that you will hear about today. Biomedical research, both basic and clinical, is a major component of this response and is the primary responsibility of the NIH. The goal of HIV/AIDS research is to provide the tools necessary to diagnose, prevent, and treat HIV disease. Several of these tools are directly applicable to the goals of PEPFAR in the developing world. In this testimony, I will first briefly describe for you the accomplishments resulting from basic, applied, and clinical research supported by NIH that have led to interventions implemented by PEPFAR, contributing to the fulfillment of its mission. Then I will

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[4] Hall H, et al. Estimation of HIV Incidence in the United States. *JAMA*. 2008;300(5): 520-529; Centers for Disease Control and Prevention (CDC). HIV Prevalence Estimates – 2006. *MMWR*. 2008;57(39):1073-1076.
[5] UNAIDS, WHO. *2009 AIDS Epidemic Update*. November 2009; 6. Available at http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2009/default.asp.
[6] UNAIDS. *UNAIDS Outlook 2010*. July 2010;12. Available at http://www.unaids.org/OUTLOOK/OutlookReport.aspx.

describe NIH HIV/AIDS research endeavors that will complement the PEPFAR mission in the future

NIH HIV/AIDS RESEARCH RESULTS THAT HAVE ADVANCED THE PEPFAR MISSION

Treatment of HIV Infection

For nearly three decades, NIH has supported much of the basic and clinical research that has led to the development and optimal clinical use of nearly 30 antiretroviral drugs, or ARVs; these medications have transformed the medical management of HIV/AIDS. First, NIH-supported basic research on HIV biology and pathogenesis enabled the development of these ARVs. Second, studies conducted by the global clinical trial networks established and supported by NIH demonstrated that combination ARV therapy is effective and helped to optimize the use of these medications. Finally, the longstanding NIH Multicenter AIDS Cohort Study and Women's Interagency HIV Study have illuminated the clinical course of HIV/AIDS and the effects of long-term treatment with ARVs, further informing the medical management of HIV/AIDS.

Domestically, ARVs have improved and dramatically prolonged the lives of people with HIV/AIDS. When I first began caring for patients with AIDS in 1981, the survival time for these individuals was about six months; now, the life expectancy of an HIV-infected patient with access to life-saving ARVs and other state-of-the-art care approximates that of uninfected individuals, according to

mathematical models.[7] With the provision of ARVs through PEPFAR and other programs that you will hear about from Ambassador Goosby and other witnesses, these lifesaving medications have now reached more than five million HIV-infected people throughout the world.

Prevention of HIV Infection

NIH research also has led to the development of important tools for the prevention of HIV infection that have been key to PEPFAR's successes. For example, NIH-supported studies helped demonstrate that condoms, when used correctly, can prevent sexual transmission of HIV. Another contribution of NIH research is in the prevention of mother-to-child transmission (PMTCT) of HIV, notably with the provision of ARVs before, during, and after birth to mothers and, in some cases, to their newborns. Using the results from NIH-supported studies, these regimens have been refined considerably over the past few years and have been used with great success in the developing world through PEPFAR's programs, saving hundreds of thousands of infants from HIV infection.

Adult male circumcision is another scientifically proven prevention tool in our armamentarium against HIV. In studies conducted in Kenya and Uganda, NIH-supported researchers demonstrated that medically supervised circumcision of adult African men reduced by more than 50 percent the risk of acquiring HIV

[7] van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F; ATHENA National Observational Cohort Study. *Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals.* AIDS. 2010; 24(10):1527-1535.

infection through heterosexual intercourse, validating many observational studies that suggested a correlation between male circumcision and a decreased rate of acquisition of HIV infection.[8,9] This protective effect has been sustained for more than three years after the procedure.[10] Adult male circumcision now is being implemented internationally as part of PEPFAR's comprehensive HIV prevention programs.

NIH has worked in close partnership with PEPFAR in the fight against HIV/AIDS since members of this Committee, including Chairmen Hyde and Lantos, first supported PEPFAR's establishment in 2003. Much has been accomplished; yet significant challenges remain in our efforts to control and ultimately end the global HIV/AIDS pandemic. Through NIH-supported research, we are addressing these challenges by exploring new and improved ways to prevent new HIV infections, to cure HIV infection, to optimize treatment regimens, to treat HIV/AIDS co-morbidities, and to support PEPFAR programs by providing innovative solutions to these challenges and through implementation science and capacity-building activities.

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[8] Bailey RC, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet*. 2007; 369(9562):643-57.
[9] Gray RH, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomized trial. *Lancet*. 2007; 369(9562):657-66.
[10] Bailey RC, et al. The protective effect of male circumcision is sustained for at least 42 months: results from Kisumu, Kenya Trial. *XVII International AIDS Conference*, 2008.

NIH HIV/AIDS RESEARCH ENDEAVORS THAT WILL HELP THE PEPFAR MISSION IN THE FUTURE

Preventing New Infections

While PEPFAR and other programs have made great strides in providing ARVs to those who need them around the world, the stark reality is that we will not be able to contain the HIV/AIDS pandemic by treatment alone. For every person who starts ARV therapy in low- and middle-income countries, two to three individuals become newly infected with HIV.[11] While numerous tools and strategies, such as those I mentioned earlier, can prevent HIV infection, these interventions are accessible only to a minority of persons at risk of infection.[12] In addition to improving access to these proven prevention tools, we need new prevention modalities if we are to implement a truly transformative HIV prevention effort and reduce HIV infections in the United States and throughout the world. Conducting and supporting basic, applied, and clinical research to develop new tools to prevent HIV infection remains one of the highest priorities of the NIH HIV/AIDS research program.

One such approach that is being pursued by NIH, other federal agencies, and nongovernmental organizations is pre-exposure prophylaxis (PrEP), which involves providing ARVs to HIV-negative individuals who are at high risk of HIV

[11] UNAIDS. *AIDS epidemic update 2009.* http://www.who.int/hiv/pub/epidemiology/epidemic/en/index.html.
[12] UNAIDS. *AIDS epidemic update 2009.* http://www.who.int/hiv/pub/epidemiology/epidemic/en/index.html.

infection, such as the uninfected partner in an HIV-discordant couple. This approach is well-established for preventing other infectious diseases, such as prophylactic administration of antibiotics to prevent certain bacterial infections. Several large PrEP clinical trials are under way, with the earliest results on safety and efficacy expected later this year. These trials also address important questions about the development of HIV drug resistance and the potential for increased risky behavior. Should this approach be proven efficacious in preventing HIV infection, one challenge in implementing PrEP is the cost of providing ARVs to those at high risk of infection at a time when it is not yet possible to treat all those who are already infected. Nonetheless, in selected populations at high risk of infection, it may be cost-effective to implement PrEP to prevent HIV infections. NIH and its partners are committed to determining the scientific and practical feasibility of PrEP as an HIV prevention tool.

One of the compelling features of PrEP is that women and other vulnerable individuals can control its use independent of their sexual partners. Safe and effective topical microbicides, such as vaginal gels, foams, and creams, represent another potentially important method of HIV prevention for women, who now often rely on male-controlled prevention modalities such as the male condom. NIH currently supports a robust research portfolio to develop topical microbicides to prevent HIV infection, to evaluate new products and formulations, as well as to establish different routes of administration.

The early clinical trials of microbicides tested candidates that had physical properties that were thought to be potentially protective. These trials, however, were not successful. After these disappointing results, researchers shifted their focus to a new generation of candidate microbicides, which utilize ARVs formulated for topical application. The first results from a large clinical trial using such a product—the CAPRISA 004 trial in South Africa—were announced this summer at the XVIII International AIDS Conference in Vienna. The CAPRISA study found that the incorporation of an ARV drug —in this case, tenofovir—into a vaginal gel was more than 50 percent protective against HIV infection, when used as directed.[13] With women constituting the majority of new HIV infections throughout the world, this finding is an important step toward empowering an at-risk population with a safe and effective HIV prevention tool. The CAPRISA study was sponsored primarily by the U.S. Agency for International Development using the clinical trial infrastructure established with NIH support.

Now we must build upon the CAPRISA trial results and optimize a highly effective and acceptable microbicide for women and others at high risk of HIV infection which could be deployed by PEPFAR and other programs. The NIH-sponsored Vaginal and Oral Interventions to Control the Epidemic (VOICE)

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[13] Center for the AIDS Programme of Research in South Africa (CAPRISA). Information site at http://www.caprisa.org/joomla/index.php/component/content/article/1/225. *See also* Karim Q et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329(5996): 1168-1174.

study, which began last fall and is expected to enroll 5,000 women in four African countries, will provide additional safety and effectiveness data for a tenofovir-based vaginal gel as an HIV prevention method. The study also will offer some insight as to the gel's acceptability as a product when used just once daily rather than both before and after sexual intercourse. Additionally, the VOICE study is examining oral ARVs (tenofovir alone or tenofovir plus emtricitabine) as an alternative HIV prevention method. Thus, this study also will enable us to evaluate the relative value of oral PrEP regimens versus topical microbicide regimens in women.

NIH also is assessing the feasibility of another ARV-based prevention approach, which is often referred to as "treatment as prevention." The "treatment as prevention" concept is predicated on mounting evidence that suggests that a reduction in levels of HIV in an infected individual can reduce HIV transmission from that individual to others. For example, a recent study of HIV-serodiscordant couples in Africa, supported by NIH and the Bill and Melinda Gates Foundation, found that treatment of the infected partner reduced the risk of HIV transmission to the uninfected partner by 92 percent.[14] Moreover, studies among communities in the developed world have shown that expanded ARV treatment and the use of

[14] Donnell D et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet.* 2010;375(9731):2092-2098.

other preventive measures to decrease the level of HIV were associated with a decrease in the number of new HIV infections.[15]

In a similar vein, NIH, CDC, and other partners are assessing the feasibility of a voluntary "seek-test-and-treat" behavioral and clinical intervention strategy to prevent HIV infection. Through this partnership, NIH is preparing a study of at-risk individuals in inner-city areas in the United States, including Washington, D.C., to evaluate the feasibility of implementing a combined strategy of expanding HIV testing, diagnosing infection early, and better linking HIV-infected patients to medical care and treatment. This strategy may be applicable to the developing world as well, although we must assess the practical challenges of implementing this approach broadly in such settings.

Finally, the most powerful prevention tool would be a safe and effective HIV vaccine. In 2009, a large Phase III efficacy trial of a "prime/boost" vaccine regimen provided the first, albeit modest, signal that a vaccine could prevent HIV infection in people.[16] This study, conducted in Thailand by the U.S. Army and the Thai Ministry of Public Health with support from NIH and other partners, has provided important new leads that we are pursuing vigorously along with other approaches in the development of a safe and effective HIV vaccine. These

[15] Wood E et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ*. 2009;338:b1649; Das M et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. *PLoS One*. 2010;5(6):e11068.

[16] U.S. Military HIV Research Program. RV144 Phase III HIV Vaccine Trial information site. Available at https://www01.hjf.org/apps/internet/hivnewscenter.nsf/phase3.

efforts include basic research to identify specific components of the virus that could potentially serve as vaccine candidates, and immune system proteins—antibodies—that target these components.

For example, the recent discovery by scientists at the NIAID Vaccine Research Center of two broadly neutralizing antibodies against HIV is especially promising.[17] Laboratory studies indicate that the newly identified antibodies can potently neutralize a larger number of HIV strains than did previously identified antibodies. The identification of these exceptionally broadly neutralizing antibodies to HIV and the structural analysis that explains how they work will contribute to efforts to find a preventive HIV vaccine for global use. Since the development of a safe and effective vaccine to prevent HIV infection would not only be an important scientific accomplishment but also would be a "game-changer" for the future of PEPFAR, we are encouraged by the potential of such research findings in this vaccine development effort.

Curing Existing HIV Infections

As mentioned above, in 2008 alone there were an estimated 2.7 million new HIV infections, most of them occurring in PEPFAR-associated and other low-income

[17] Wu X *et al.* Rational design of envelope surface identifies broadly neutralizing human monoclonal antibodies to HIV-1. *Science.* DOI: 10.1126/science.1187659 (2010); Zhou T *et al.* Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. *Science.* DOI: 10.1126/science.1192819 (2010).

countries.[18] Despite the enormous progress made by PEPFAR in providing ARVs to HIV-infected individuals in the developing world, in low- and middle-income countries, only 30 to 40 percent of people in need of such therapy are receiving it.[19] While ARV regimens have been dramatically successful at saving lives and restoring health, these drugs must be given for the remainder of a patient's life.

This situation is unsustainable both financially and operationally. One way to address the problem is to prevent new HIV infections. Another way is to cure existing HIV infections, allowing cured individuals to discontinue ARV therapy. While it may not be possible to cure all infected individuals worldwide, a cure for HIV in some proportion of HIV-infected individuals would ultimately have a dramatic impact on controlling the pandemic.

Despite our substantial progress in understanding HIV/AIDS and treating it with ARV medications, a cure for HIV/AIDS that would induce permanent remission in the absence of drug therapy has remained frustratingly out of reach. Research aimed at eliminating HIV from the body has been unsuccessful, largely because HIV is unlike virtually any other pathogen in its singular ability to hide from the body's immune system. HIV evades ARV therapy by shielding itself in latent cellular "reservoirs" that are rapidly established after initial infection. Even in

[18] UNAIDS, WHO. *2009 AIDS Epidemic Update*. November 2009; 6. Available at http://www.unaids.org/en/KnowledgeCentre/HIVData/EpiUpdate/EpiUpdArchive/2009/default.asp.
[19] WHO. *Antiretroviral therapy*. http://who.int/hiv/topics/treatment/en.

patients who have received ARV medications for a decade or more, we cannot fully purge the virus from these hiding places. If therapy is discontinued or interrupted, the virus invariably re-emerges from its reservoirs and begins replicating vigorously.

A cure for HIV infection might take one of two approaches. First, we may be able to completely eradicate the HIV reservoirs in the body; this is referred to as a "sterilizing" cure. Second, and more likely, we may be able to shrink HIV reservoirs to the point that a rebound of virus replication and the appearance of virus in the bloodstream do not occur, even after the withdrawal of ARV medications. This is a so-called "functional" cure, or permanent suppression of viral replication without eradication. A functional cure is probably most feasible in patients who are treated early and aggressively after the onset of HIV infection—in these individuals, the HIV-specific immune response is likely to still be intact. NIH is actively supporting research to find a cure for HIV disease. Much of this research, both fundamental and clinical, is aimed at better understanding where reservoirs of HIV are located, how they are established and maintained, and how to eliminate them.

Optimizing Treatment Regimens and Treating Co-morbidities

Tens of millions of HIV-infected individuals likely will depend on antiretroviral medications and other therapies for many years. To help these people, NIH is committed to research to optimize treatment of HIV/AIDS and its associated

infections and co-morbidities. For example, NIH supports studies to evaluate strategies for the best use of existing ARVs in combination with other drugs, including ways to minimize drug-related complications. Many new and improved HIV treatment strategies, as well as preventive strategies, are tested through the longstanding NIH HIV/AIDS Clinical Trial Networks, which have led to many of the medical advances that are being successfully implemented by PEPFAR today. The awards supporting the six current clinical trial networks will expire in 2013 and 2014. Building on the success of the current infrastructure, NIH is looking to expand the scope of the networks' activities to include studies of other infectious diseases of significance to people who are infected with HIV or are at risk for infection, especially tuberculosis (TB).

TB is a very serious co-morbidity for HIV-infected individuals and accounted for nearly a quarter of HIV-related deaths worldwide in 2008.[20] Improving the effectiveness of the standard therapeutic protocol for HIV-TB co-infection and developing more sensitive TB diagnostics will help programs such as PEPFAR save lives and improve clinical outcomes. Promising results from the recent Cambodian Early versus Late Introduction of Antiretroviral Drugs (CAMELIA) trial, funded by NIH and the French National Agency for Research on AIDS and Viral Hepatitis, indicate that it is possible to prolong the lives of untreated HIV-infected adults with very weak immune systems and newly diagnosed TB by

[20] World Health Organization. Tuberculosis and HIV factsheet. Available at http://www.who.int/hiv/topics/tb/en/index.html.

starting HIV therapy two weeks after beginning TB treatment, rather than waiting eight weeks, which had been the standard of care.[21] This finding brings physicians closer to optimizing the treatment of severely immunocompromised individuals co-infected with HIV-TB.

Implementation Science

Implementation science is the translation of evidence-based findings from efficacy trials, such as those routinely supported by NIH, into at-scale population-level practices. While implementation science is not our primary mandate, NIH is collaborating with PEPFAR and its partners to conduct studies that address the "research-to-practice" gap. For example, with support from PEPFAR, NIH is sponsoring a number of implementation research projects through supplemental awards to NIH grantees who already are conducting research at PEPFAR sites. These studies will assess the efficiency, effectiveness, and impact of PEPFAR programs such as PMTCT and adult male circumcision and provide insights into how proven interventions can be brought to scale.

Capacity Building and Training

In addition to the research and development of new and improved tools and strategies for the prevention, diagnosis, and treatment of HIV/AIDS, NIH

[21] F.X. Blanc, T. Sok, D. Laureillard, et al. Significant enhancement in survival with early (two weeks) vs. late (eight weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis. *XVIII International AIDS Conference*. July 18-23, 2010. Vienna. Abstract THLBB106.

contributes to PEPFAR by building global research and clinical capacity, developing a cadre of skilled in-country partners, and expanding the ranks of skilled health personnel in PEPFAR countries. For example, NIH recently announced a new initiative to strengthen medical education in sub-Saharan Africa, in collaboration with PEPFAR. The *Medical Education Partnership Initiative* —a joint effort of the Office of the Global AIDS Coordinator, the Health Resources and Services Administration, CDC, the Department of Defense, and NIH—will support PEPFAR's goal to increase the number of new health care workers in this area. This program also will serve the related objectives of strengthening host-country medical education systems and enhancing clinical and research capacity in Africa.

Conclusion

The basic, applied, and clinical HIV/AIDS research supported by NIH has played a critical role in the response of the U.S. Government to the HIV/AIDS pandemic through PEPFAR and the GHI. The results of NIH-supported research—for example, the research, development, and optimization of ARVs; prevention of mother-to-child transmission; and the proven efficacy of medically supervised adult male circumcision—have provided the tools for global HIV/AIDS programs on the ground that have already saved millions of lives.

While we have accomplished much since those first AIDS cases nearly three decades ago, much remains to be done if we are to control and ultimately end

the global HIV/AIDS pandemic. As we endeavor to prevent new infections, cure existing infections, and optimize treatment of HIV and its co-morbidities, I firmly believe that basic, applied, and clinical research will continue to form the foundation for these efforts.