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The Role of NIH Biomedical Research in the Development of an HIV Vaccine

Statement of

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Mr. Chairman and members of the Committee, thank you for giving me the opportunity to discuss the ongoing efforts of the National Institutes of Health (NIH) to develop a safe and effective vaccine for the prevention of human immunodeficiency virus (HIV) transmission. Today I will first briefly outline the daunting scientific barriers that must be overcome to develop such a vaccine, and then describe some of our domestic and global HIV vaccine research and development programs, including a major new international initiative to foster global collaboration and cooperation in research leading to the development of an HIV vaccine.

Approximately 40 million people worldwide are now living with HIV/AIDS. Sub-Saharan Africa is the hardest hit, with more than 25.4 million people infected. South and South-East Asia together account for more than 7.1 million infected people, with 1.4 million more in Eastern Europe and Central Asia, 2.1 million in Latin America and the Caribbean, 1.1 million in East Asia, 1 million in North America, 610,000 in Western and Central Europe, and 35,000 in Oceania. Approximately 14,000 people worldwide are newly infected with HIV *every day*.

The first line of defense against any disease, and particularly an infectious disease pandemic, is prevention. Fortunately, we have proven ways to prevent HIV transmission. For example, in addition to the role that certain antiretroviral drugs play in the treatment of HIV-infected individuals, drug regimens have also been shown to dramatically reduce the risk of HIV transmission from mother to

child in both developed and developing countries. Moreover, the risk factors associated with HIV transmission have been well defined, and prevention programs are operating to some extent in most nations of the world. In virtually all developed nations and in certain developing countries such as Uganda, Brazil, and Thailand, these prevention programs have proven effective in slowing the spread of the virus. Interventions that have been employed successfully include mass media campaigns; voluntary HIV testing and counseling; screening of donated blood; education and outreach to at-risk populations; behavioral modification programs, such as the promotion of abstinence and fidelity; abbreviated courses of antiretroviral drugs to prevent mother-to-child transmission of HIV; treatment for drug abuse, which could include measures to reduce the sharing of contaminated injecting equipment by injection drug users; and condom distribution. Missing from this arsenal of preventive tools, however, is an effective vaccine.

Historically, vaccines have led to some of our greatest successes in the fight against infectious diseases, including the eradication of smallpox, the near eradication of polio, and enormous reductions in the disease burden imposed by measles, mumps, hepatitis, influenza, diphtheria, and many other infections. For virtually all infections, particularly viral infections, if the patient does not die, the immune system ultimately clears the infection and the person is immune to subsequent exposure to the infectious agent, sometimes for life. An effective vaccine preparation only needs to mimic the effect of natural infection on the

immune system to prevent infection and/or disease upon exposure to the infectious agent in question.

Smallpox, for example, was a terrible disease, but most patients survived and were protected thereafter by lifelong immunity. In 1796, Edward Jenner demonstrated in England that smallpox could be prevented by inoculation of a person with material from a cowpox lesion. This finding led to the development of a modern smallpox vaccine which was deployed globally in a massive campaign in the 1960s to eradicate smallpox from the human population, a goal that was achieved in 1979. Jenner's smallpox vaccine, like the modern equivalent, was based on a live virus that was closely related to the virus that causes smallpox but that did not cause illness. Vaccination primed the immune system to fend off infection if the person subsequently was exposed to the virulent smallpox virus. The Salk vaccine against polio, which became available in 1955, was based on a killed polio virus. Injection of the inactivated virus alone was sufficient to provoke an immune response that mimicked natural immunity and was capable of blocking infection upon exposure to the live, virulent virus.

The scientific challenges that must be solved to develop an effective vaccine against HIV have proven more daunting than those challenges that scientists had faced previously. Perhaps the biggest obstacle is that immune-mediated eradication of HIV from the body, with subsequent naturally induced immunity, simply does not occur. Even after more than 60 million cumulative HIV infections

since the beginning of the pandemic, there never has been a documented case in which a person with established HIV infection has completely eliminated the virus from his or her body. The fact that the immune system is apparently never able to defeat HIV on its own makes it more difficult for scientists to develop a way to induce a protective immune response. In other words, a vaccine that mimics natural infection will likely not be good enough. It must do better than natural infection in inducing what should ultimately be a protective immune response.

We have gained a solid, if incomplete, understanding of how HIV evades and ultimately defeats the immune response. First, because the primary target of its devastation is the immune system itself, HIV disables the very cells that are responsible for fighting it. Second, HIV is a retrovirus, which means that it can integrate its viral sequence into the chromosomes of infected cells. Thus, the virus can shield itself from immune attack for many years, only to emerge when the infected cell is activated by the immune system to fight another infection. Third, HIV conceals the protein components that can induce a protective immune response, and therefore presents itself to the body in a way that makes it difficult for the immune system to respond effectively. Fourth, HIV is genetically diverse and rapidly changing, especially in its outer coat proteins; its mutability allows HIV to evade the modest protective responses the immune system is naturally able to make.

All of these factors combine to create a scientific challenge as difficult as any we have ever confronted in infectious disease research. I do not believe it is an insurmountable problem, however, and we are doing everything in our power to meet this daunting challenge. Our activities include a strong program of basic research on HIV and the immune system, multiple initiatives to create and test new vaccine candidates, and development of a large, international network of clinical research sites through which vaccine candidates are evaluated. NIH leads the Federal effort for the development and evaluation of HIV vaccine candidates; the U.S. Centers for Disease Control and Prevention, the Department of Defense, and other Federal agencies collaborate in this effort. In budgetary terms, the President's Budget request for fiscal year (FY) 2006 for HIV/AIDS research at NIH is $2.9 billion. Of this, $607 million is for vaccine research and development; this figure represents a nearly six-fold funding increase for vaccine research over the past ten years and accounts for the majority of global HIV vaccine development spending worldwide. In fact, the NIH HIV vaccine program represents the largest public investment in HIV vaccines in the world.

Development of a successful HIV vaccine candidate rests upon a foundation of basic research on the virus itself, including how it attacks the human immune system, and how the immune system responds to HIV infection. Since the earliest days of the pandemic, researchers have applied what they had learned about the virus to create vaccine candidates, which then were tested in both

animals and human volunteers. In the 21 years since HIV was first identified as the cause of AIDS, we have made considerable progress not only on these basic HIV research questions, but also in our overall understanding of the structure and function of the immune system.

These advances are now allowing us to pursue new vaccine strategies, and create new vaccine candidates that would have been impossible even a few years ago. In the early years of the pandemic, vaccine development efforts focused primarily on humoral immunity, that is, on the induction of specific antibodies that could neutralize the virus. From these studies, scientists discovered that it is extraordinarily difficult to raise antibodies that neutralize the many strains of the virus that circulate in the world. Because of this difficulty, development efforts have focused more recently on cell-mediated immunity, which, in general, does not protect against initial infection but can stop progression of disease in animal models. The leading candidates that induce primarily cell-mediated immunity are now or will soon be in clinical trials that will determine whether this approach may have an impact on infection or disease progression. Researchers are now turning their attention to the identification of new vaccine candidates based on strategies that induce both humoral and cell-mediated immunity.

Clinical testing of candidate vaccines is a key component of vaccine development. Once a candidate vaccine has been developed in a pre-clinical

setting, the process by which the vaccine is tested in humans requires three distinct phases of evaluation. Phase I trials are the first human tests of a candidate vaccine, generally conducted on small numbers (10-30) of healthy adult volunteers. The main goal of a Phase I trial is to evaluate safety and, to a lesser extent, to evaluate the immune responses evoked by the vaccine. In addition, different vaccine doses and immunization schedules are compared. Phase II testing involves a larger number of volunteers (50-500) and is designed to generate additional safety data as well as information to refine the dosage and immunization schedule. Occasionally, preliminary efficacy data are gathered from Phase II studies. Phase III trials are the definitive test of whether a vaccine is safe and effective in preventing disease; these trials involve thousands of volunteers. Successful demonstration of efficacy in a Phase III trial can lead to an application for licensure of the vaccine. These three phases take several years to complete.

Because most HIV infections occur in developing nations, HIV vaccine testing must in large part be carried out internationally. Many of the countries most affected by the HIV pandemic, however, have few resources and, in many cases, have virtually no public health or medical care delivery infrastructure. NIH has therefore developed an extensive network of clinical research sites in partnership with thirteen countries worldwide that are capable of conducting rigorous and ethically sound clinical trials of candidate vaccines. Since the 1980s, NIH has conducted a total of 85 clinical trials of candidate HIV vaccines in the United

States and worldwide, involving more than 18,000 human volunteers. The majority of these trials have been Phase I immunogenicity and safety trials; nine such trials are currently underway. Others are larger Phase II studies designed to gather further safety data while beginning to shed light on possible efficacy. One large Phase III trial currently underway is testing a two-pronged "prime-boost" strategy of two candidate vaccines that in combination induce immune responses quantitatively and qualitatively different from those induced by either component alone. Only one other candidate HIV vaccine, AIDSVAX, has undergone a Phase III trial, and it unfortunately did not prevent HIV infection.

A few years ago, it became apparent that although the scientific research base was expanding rapidly and substantial resources were being devoted to HIV vaccine research by the U.S. government, international coordination of and support for HIV vaccine development efforts could be improved. In 2003, a group of scientists, of which I was a member, proposed the creation of a "Global HIV Vaccine Enterprise" to foster collaboration, cooperation and transparency in the conduct of HIV vaccine research on a global scale. The proposal, published in the journal *Science*, called for the creation of a "virtual consortium" of independent government and non-government organizations committed to accelerating the development of a preventive HIV vaccine. President Bush proposed this concept of a Global HIV Vaccine Enterprise to the G8 meeting of industrialized countries in June 2004, which endorsed it unanimously.

Since then, the Global HIV Vaccine Enterprise has continued to grow and mature. It is important to note that the Enterprise is *not* a distinct organization with a hierarchical structure and formal leadership, nor is it a multi-national fund that centrally administers pooled resources. Instead, Enterprise partners will advance HIV vaccine research and development through the shared implementation of a globally developed strategic plan, mobilization of increased resources for vaccine development, and greater collaboration among researchers from participating organizations. The overarching purpose is to efficiently bring resources to bear on the gaps in HIV vaccine research, while at the same time allowing for flexibility in how research is carried out by the various participants.

The strategic plan that will guide the Enterprise was published online in January 2005 in the journal *Public Library of Science Medicine*. Importantly, the plan concludes that the major difficulties encountered in the development of an HIV vaccine are scientific. The plan proposes five major activities to address the scientific priorities: (1) creation of HIV vaccine development centers or consortia to address the key scientific obstacles; (2) creation of a network of individuals and companies with vaccine manufacturing expertise to facilitate advancement of improved candidates; (3) development of a global system of laboratories that will standardize laboratory evaluation parameters; (4) sharing of common reagents; and (5) development of a network of clinical research training centers, all with the full engagement of scientists from developing countries.

At the same time the President sought and obtained G8 endorsement of the Enterprise, he announced that NIH would fund a major new research initiative, called the Center for HIV/AIDS Vaccine Immunology, or CHAVI. This initiative builds on existing Federal HIV vaccine research efforts, such as the Dale and Betty Bumpers Vaccine Research Center (VRC) located on the NIH campus in Bethesda, MD. Five years ago, NIH inaugurated the VRC, a single state-of-the-art facility that brings together scientists with different areas of expertise critical for rapid development of vaccines against HIV and other infectious diseases. The research scope of the VRC encompasses all stages of vaccine development, including basic research; design and development of vaccine candidates; preclinical testing; production of vaccine candidates; and conduct of human clinical trials to determine vaccine safety and efficacy. To date, the VRC has conducted or supported twelve Phase I HIV vaccine clinical trials. A VRC vaccine candidate designed to protect against the three major classes of the virus in the world will advance to Phase II clinical testing in the United States, Africa, South America, and the Caribbean in the coming year.

CHAVI is based on the VRC model, but with two key differences: CHAVI will be dedicated entirely to HIV vaccine research, and unlike the “bricks and mortar” VRC, CHAVI will be a “virtual center” that will link scientists at multiple sites into a single functional unit. The mission of CHAVI will be to support intensive, coordinated, and multi-faceted approaches to address key immunological

roadblocks to the discovery and development of a safe and effective HIV vaccine, as defined by NIH and as identified by the strategic plan of the Global HIV Vaccine Enterprise. We are now evaluating several very strong applications from groups of leading HIV researchers, and we expect to make an award this fiscal year. Funding for CHAVI will be provided for seven years; the award will be approximately $14 million in FY 2005 for start-up costs; funding for FY 2006 is estimated to be as much as $49 million.

In closing, Mr. Chairman, I look to the future of the HIV pandemic with both deep concern and great hope. Concern, because as bad as the situation is now, unless we can change the trajectory of the pandemic it will certainly become much worse. Hope, because I am optimistic that a successful vaccine candidate will eventually emerge, even though the scientific barriers to success are such that I cannot say when that day will come. In fact, success is likely to be only incomplete at first, and a partially effective vaccine will have to be studied and refined. Meanwhile, we at NIH will do everything in our power to successfully address as rapidly as possible the complex scientific obstacles to the development of an HIV vaccine.

Thank you for this opportunity to testify before you today, and I would be happy to answer any questions that you may have.