



Testimony
Committee on Oversight and Government Reform
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The Role of NIH Research in HIV Prevention

Statement of

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Mr. Chairman and members of the Committee, thank you for giving me the opportunity to discuss the research efforts of the National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services, with regard to the prevention of human immunodeficiency virus (HIV) transmission. I am the Director of the National Institute of Allergy and Infectious Diseases (NIAID), one of the many Institutes and Centers of NIH that support research on HIV prevention. The NIH supports a broad portfolio of HIV/AIDS research, including prevention research to understand the factors that lead to HIV acquisition as well as studies to develop evidence-based interventions—both biomedical and behavioral—to prevent transmission of HIV. The President's Budget request for fiscal year 2009 for HIV/AIDS research at NIH is \$2.9 billion, with more than \$1.1 billion allocated for HIV prevention research.

In the quarter century since HIV was identified as the cause of the acquired immune deficiency syndrome (AIDS), we have made extraordinary progress in understanding the disease-causing mechanisms—or pathogenesis—of HIV/AIDS. That this research has led to the development of numerous drugs to treat HIV/AIDS is perhaps the greatest success story in NIH-funded AIDS research. NIH-supported research helped make possible the more than 25 antiretroviral drugs (ARVs) that have transformed HIV/AIDS in the United States from an almost uniformly fatal disease into a manageable chronic condition. While only 30 percent of people throughout the world who should be receiving ARVs according to standard treatment guidelines are receiving them, the heroic efforts of many organizations and individuals are making progress in providing access in the developing world to life-saving drugs for those infected with HIV.

Yet despite our accomplishments in the area of treatment, HIV/AIDS continues to exact a staggering toll. An estimated 33 million people worldwide are infected with HIV, and approximately 2.7 million people were newly infected with HIV in 2007, according to UNAIDS. In low- and middle-income countries for every person who commenced antiretroviral therapy in 2007, approximately 2.5 people were newly infected. Clearly, we cannot end the HIV/AIDS pandemic without preventing new infections. The first line of defense against any disease, and particularly an infectious disease pandemic, is prevention.

While the situation in the developing world dramatically illustrates this point, the need for prevention also applies to the epidemic here in the United States, where approximately 56,300 new HIV infections occurred in 2006, according to recent estimates from the Centers for Disease Control and Prevention (CDC). Among at-risk groups, men who have sex with men (MSM) comprise the greatest proportion—53 percent—of these new infections. African-Americans are impacted more than any other racial or ethnic group, accounting for 45 percent of the new infections in 2006, even though they account for only 12-13 percent of the U.S. population. The new data do not indicate an actual increase in the annual number of new HIV infections, but reflects a more accurate way of measuring new infections. A CDC historical trend analysis has suggested that the annual number of new infections has remained fairly stable for the last decade.

NIH Prevention Research

The NIH supports a broad portfolio of HIV prevention research that includes basic, translational, and clinical research on biomedical interventions for HIV infection as well as basic, translational, and clinical behavioral and social sciences research associated with HIV risk, transmission, and acquisition. The highest priority of NIH for HIV/AIDS research is to expand the range of modalities for preventing HIV transmission beyond those that are currently available.

The federal investment in HIV research over the last two decades has generated a number of successes in the area of prevention; for example, we have proven interventions and strategies to prevent HIV transmission. Moreover, the risk factors associated with HIV transmission have been well defined, and prevention programs have been implemented 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 HIV pandemic. Interventions implemented with varying levels of success include courses of ARVs to prevent mother-to-child transmission of HIV; education and outreach to at-risk populations; behavioral modification programs, such as the promotion of abstinence, fidelity and condom use; voluntary HIV testing and counseling; treatment for drug abuse (including drug abusers in the criminal justice system); mass media campaigns; screening of donated blood; and condom distribution.

Coordination with CDC

NIH works closely with its sister agency, CDC, in coordinating NIH's behavioral and biomedical prevention research activities with the prevention activities of CDC. For example, NIH worked closely with the CDC to develop a Program Announcement, released in May 2008, to encourage applications in dissemination, implementation, and operational research for HIV prevention. NIH and CDC are represented on each other's advisory councils and on other working groups, participating in the processes to set priorities for the two agencies, including in the area of HIV prevention. In addition, NIH and CDC collaborate directly on prevention research. For example, NIH and CDC are collaborating on a trial evaluating the use of rapid testing and counseling in drug abuse programs. Lastly, NIH program staff are in frequent contact with CDC program staff on a more informal basis, keeping CDC informed about findings of NIH-supported HIV prevention research.

Prevention of Mother-to-Child Transmission

Mother-to-child transmission of HIV, which can occur during pregnancy, childbirth, or through breastfeeding, accounts for more than 90 percent of all cases of childhood HIV infection, especially in countries where effective ARVs are not readily available. In addition to the role that certain ARVs play in the treatment of HIV-infected individuals, drug regimens have also been shown to reduce dramatically the risk of HIV transmission from mother to child. In the United States and other developed countries, provision of ARVs to prevent mother-to-child transmission has reduced perinatal HIV infection rates to less than one to two percent. The NIH-supported HIVNET 012 study

demonstrated that a single dose of nevirapine given to the mother at the onset of labor and a single dose of nevirapine given to the infant within 72 hours after birth reduced dramatically the risk of perinatal transmission. This regimen has been adopted as the standard of care in many resource-poor countries; however, widespread implementation has been limited. In 2007, NIH-supported studies provided more tools for the prevention of mother-to-child transmission in developing countries. This year, combined results from the SWEN study conducted in Uganda, Ethiopia, and India and the PEPI study in Malawi showed that extended courses of daily nevirapine administered to newborns decreased further HIV transmission via breastfeeding and reduced mortality. The development of safe, simple, and inexpensive interventions that would be more globally applicable, including those to reduce transmission during breastfeeding, remains a high priority for the NIH and is the subject of ongoing research.

Behavioral Interventions

A critical component of NIH prevention research is the development and testing of behavioral interventions. These interventions may be focused on men, women, and adolescents at high risk of acquiring HIV (primary prevention) or they may be directed toward persons living with HIV to reduce the risk of their transmitting HIV to others (secondary prevention). In addition, NIH supports research to better understand the sociocultural context of HIV risk or protection, particularly in communities at high risk of HIV acquisition.

Data summarized from over one hundred intervention trials—with participants numbering in the tens of thousands—indicate that behavioral modification strategies are effective in increasing condom use, delaying initiation of sexual activity in adolescents, and reducing acquisition of sexually transmitted diseases (STDs); these outcomes are frequently used in behavioral intervention trials as a surrogate for HIV transmission. One such NIH intervention trial, Project Light, was conducted at 37 urban STD clinics in five U.S. cities, with blacks comprising 74 percent of the study participants. This randomized clinical trial compared a seven-session cognitive-behavior intervention with the provision of standard HIV/AIDS information and a video. The Project Light intervention resulted in a 50 percent reduction in new gonorrhea cases among men and an increase in condom use. Modeling of HIV infections prevented by the intervention estimated a 40 percent reduction in primary infections—12 HIV infections were averted per 1,000 male participants; for females, 3 infections per 1,000 participants were averted. NIH produced a toolkit and instructional CD-ROM to facilitate dissemination of this intervention, and the intervention materials are also available through the CDC. This research effort is an example of many behavioral interventions that NIH has been able to “hand off” to the CDC for dissemination and implementation by community-based organizations and state and local health departments across the United States. The NIH behavioral research program places a high priority on addressing at-risk groups in the United States, including racial and ethnic populations. For example, NIH-supported studies demonstrated the effectiveness of a four-session intervention for women of color who lived in public housing, where rates of pregnancy and sexually transmitted infections were high. This study not only demonstrated the effectiveness of

this community-level intervention, but also included the development of training manuals and resource materials for its implementation.

NIH will soon begin enrollment of 2,000 black MSM in a study of a multi-component intervention package. The components of the experimental intervention package include HIV counseling, testing, and referral for care; STD testing and referral for care; screening for substance abuse and mental health issues and referral for care; and engagement with peer health navigators to facilitate actual uptake of health care referrals by participants. This pilot study will examine the feasibility and acceptability of the intervention in preparation for a large-scale community-level randomized trial to test the efficacy of the intervention in reducing HIV incidence, as opposed to surrogate outcomes such as STD infection.

Prevention of HIV Transmission among Drug Users

Behaviors associated with drug abuse are important factors in the spread of HIV infection in the United States. Early in the epidemic, drug abuse and HIV infection were typically connected in people's minds with infection via injection drug use and needle sharing; however, this view greatly underestimates the impact that drug and other substance abuse can have on the spread of HIV/AIDS through the dangerous risk behaviors it engenders. Drug and alcohol intoxication affect judgment and can lead to risky sexual behaviors that place people in danger of contracting or transmitting HIV.

The new CDC data indicates that HIV infections among injection drug users declined overall by 80 percent between 1988-1990 and 2003-2006. This success can be attributed to a focus on drug abuse intervention and treatment. In addition to providing a substitute for injection drug use, drug treatment programs provide a good setting for reaching IDUs and their partners with HIV prevention and care messages and interventions. These programs also can be a bridge to other needed services, such as primary health care, mental health, or other social services. Numerous studies, primarily focused on methadone maintenance treatment, have shown that substance abuse treatment programs can have a dramatic effect on HIV transmission among opiate injectors, reducing their risk as much as four- to six-fold. Drug abuse treatment works principally because it helps IDUs decrease the number of injections or helps them stop injecting altogether. Furthermore, less drug use leads to fewer drug-related risk behaviors, and that, in turn, leads to fewer exposures to HIV. Among non-injection cocaine users, drug treatment has also been shown to decrease cocaine use from an average of ten days per month at baseline to one day per month at six months. Reduction in cocaine use was associated with an average 40 percent decrease in HIV risk across gender and ethnic groups, mainly as a result of fewer sexual partners and less unprotected sex.

The Community-Based Outreach Model was designed to reach out-of-treatment IDUs who are unable or unwilling to stop using and injecting drugs and who cannot or will not access drug treatment. Compared to those in treatment, out-of-treatment IDUs are at significantly greater risk of HIV and other infections because they are more likely to

inject drugs more frequently; to share drugs, syringes, and other injection equipment; and to practice unsafe sex while under the influence of drugs. The ongoing outreach program attempts to reduce HIV risk through education on the risk factors for HIV transmission and by teaching effective skills in reducing those risks.

Adult Male Circumcision

Another HIV prevention strategy that has been proven effective is male circumcision. NIH-supported researchers in Kenya and Uganda demonstrated that medically supervised adult male circumcision reduced by more than 50 percent the risk of heterosexual African men becoming infected with HIV, validating many observational studies that saw a correlation between male circumcision and a decreased rate of HIV infection. This protective effect is sustained for more than three years after the procedure. The public health impact of increased access to male circumcision is predicted to be most pronounced in those areas with low rates of male circumcision and high rates of heterosexually transmitted HIV. Adult male circumcision is beginning to be implemented internationally as part of the President's Emergency Plan for AIDS Relief (PEPFAR), and CDC is conducting a demonstration project to assess the feasibility and acceptability of adult voluntary circumcision as a risk reduction strategy for high risk heterosexual men in the United States.

Prevention and Treatment of Co-infections

Although it seems counterintuitive, HIV is a virus that thrives in situations where the host's immune system is activated. In particular, there is considerable evidence of a

link between other infectious diseases (e.g. STDs, malaria, and tuberculosis) and an increased susceptibility to HIV infection or a rapid progression of HIV disease. As such, one potential strategy to prevent HIV infection is to treat the coinfections that activate the immune system and create a permissive environment for HIV replication; however, this strategy is still in the conceptual phase. An NIH-supported study found that the use of acyclovir to suppress herpes simplex virus 2 did not decrease HIV acquisition. Despite these results, treatment of HIV coinfections as well as the use of vaccines to prevent coinfections are active areas of study by many NIH-supported research groups.

Antiretroviral Therapy as Prevention

Strategies for the prevention of mother-to-child transmission are one example of how the ARVs that are so effective in treating HIV disease can also be used to prevent disease. Another proven intervention that uses antiretroviral drugs is Post-Exposure Prophylaxis (PEP) after occupational and non-occupational exposures to HIV. Data from NIH-supported research informed the development of the 2005 federal guidelines that recommend that ARVs be administered within 48–72 hours after exposure and continued for 28 days to reduce the likelihood of HIV acquisition.

One promising area of prevention research is the concept of Pre-Exposure Prophylaxis (PrEP), or administration of a daily dose of ARVs to individuals who are at an increased risk of HIV infection. This strategy is based on the concept that if HIV replication can be inhibited immediately following exposure to the virus, that permanent infection might be

thwarted—an effective strategy for other infectious diseases, such as malaria, and in preventing the transmission of HIV from mother to infant. Studies in animals suggest that this approach might be feasible. Multiple clinical studies of PrEP are underway in the United States and in different populations around the world, sponsored by a number of governmental and nongovernmental organizations. For example, NIH and the Bill and Melinda Gates Foundation are sponsoring a study in the United States and at international sites to test the preventive effect of antiretroviral drugs in conjunction with safe sex counseling and condom use among HIV-seronegative MSM. As data become available from this and other studies, we will understand more about the promise of this approach, including how it affects drug resistance and how it might impact risk behavior.

Another important aspect of HIV prevention is that of secondary prevention—rather than preventing HIV-seronegative individuals from acquiring HIV, the goal is to prevent HIV-infected individuals from transmitting virus to others. Certainly, behavior plays a major role in secondary prevention, but biomedical interventions may assist in these efforts. This might be achieved by reducing the viral load of HIV-infected individuals as a means of rendering these persons less infectious. The most direct way to accomplish this may be through treatment with ARVs such that viral levels are reduced to undetectable levels. Thus far, data are inconclusive as to whether HIV-infected individuals who are receiving ARV therapy and have undetectable levels of virus are still capable of transmitting HIV to uninfected partners and what level of risk, if any, this poses; this question remains an important area of study.

An important component of ARV treatment as a means of secondary prevention is promoting adherence to treatment regimens. NIH also supports behavioral intervention research to assist HIV-infected persons in adhering to HIV treatment regimens. Data from multiple studies indicate that these interventions are effective; participants receiving these interventions are 50 percent more likely to report 95 percent adherence to treatment regimens and 25 percent more likely to achieve an undetectable viral load than participants in the control arm of the studies.

Microbicides

One of the most urgent needs in the area of HIV prevention is for microbicides to prevent HIV transmission. Microbicides may be especially important for women who are otherwise dependent on male-controlled prevention strategies, such as male condoms. Research on microbicides is one of the highest priorities for the NIH. Thanks to multiple governmental and nongovernmental sponsors, the research in this field is very active. According to the Alliance for Microbicide Development, there are ongoing clinical trials on a dozen candidate products, and preclinical testing is underway on more than 50 other potential products. For example, an NIH-supported Phase II/IIb safety and effectiveness trial of two different microbicide candidates is scheduled to end this month. In addition, NIH, through its Microbicide Trials Network, is preparing to launch the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, which is a Phase IIb study that will compare a daily pill combining two ARVs to an ARV-based vaginal gel to prevent HIV transmission.

While new products continue to enter the microbicide candidate pipeline, the development of microbicides poses significant challenges. Last year, two Phase III efficacy trials of a candidate microbicide, cellulose sulfate, were stopped due to safety concerns. Other trials have failed to show product effectiveness or have identified participant lack of adherence to the investigational product as a concern. Suboptimal product adherence can compromise clinical trials; attention to other behavioral issues, such as participant behavior during the trial, will also be critical in the accurate interpretation of future trials that combine behavioral and biological prevention approaches. NIH will continue to pursue research to define markers of protection and safety for microbicide use and will continue to examine carefully all ongoing microbicide trials for safety. Our focus for further development of microbicides will continue to be on candidate products with strong safety profiles and potential for protection.

Vaccines

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 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. For example, 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.

For HIV, a vaccine that mimics natural infection will likely not be good enough because despite our considerable success in treating HIV infection and improving the length and quality of life for people living with HIV, there is no well-documented case of anyone being truly cured of HIV disease. In addition, except in rare cases, the body seems incapable of mounting an effective immune response that blocks the progression of disease in the absence of antiretroviral therapy. Thus, in order to induce a protective immune response, an HIV vaccine must do better than natural infection. Thus far, this has proven to be one of the most difficult scientific challenges ever confronted in infectious disease research. Last September, two clinical trials of a promising HIV vaccine candidate were halted after the vaccine failed to show efficacy. Since then, NIH and HIV vaccine researchers have held intensive consultations at the NIH-sponsored HIV Vaccine Summit in March 2008 and other forums to discuss the way forward for HIV vaccine research and development. These experts concluded that the balance between fundamental discovery research and vaccine development should shift toward basic discovery. To this end, NIH recently announced a new initiative to spur fundamental research that will contribute directly to the development of an HIV vaccine as well as to encourage the participation of investigators from an array of life sciences disciplines in this endeavor.

The ultimate goal of an HIV vaccine is to prevent infection. However, we must also recognize that even a vaccine that does not prevent infection but significantly alters the course of disease or the infectivity of the individual could have a positive impact on both individuals and the community. I remain cautiously optimistic that, despite recent setbacks, we will eventually have a vaccine that will be an effective tool in controlling the HIV pandemic.

Conclusion

Despite the progress we have made in the treatment of HIV disease, the worldwide scope of the pandemic paints a grim picture. Here in the United States, the number of new infections each year has been roughly stable. While we have amassed a number of proven prevention strategies for HIV, both biomedical and behavioral, the numbers speak for themselves and illustrate the need for new and improved interventions to prevent HIV transmission. New prevention interventions should include the combination of biomedical advances with effective behavioral strategies to prevent HIV, providing a comprehensive approach that addresses both biological risk as well as the behavioral and social factors that contribute to HIV infection.

It is likely that no single prevention strategy or intervention method being developed by NIH and our sister agencies and nongovernmental partners will be 100 percent effective in preventing HIV infection. Instead, we must confront this disease with multiple effective interventions, assembling a comprehensive prevention toolkit that may include vaccines, topical microbicides, circumcision, and behavioral interventions, such as

abstinence, fidelity, and condom use, depending on the target population. Only then will we be successful in effectively controlling the HIV pandemic both domestically and globally.