SEXUALLY TRANSMITTED INFECTIONS

Sexually transmitted infections (STIs), also commonly referred to as sexually transmitted diseases (STDs), are a major health problem in the United States. They are also considered to be a critical global health priority because of their relationship to HIV/AIDS and the devastating impact they have on women and infants. It is estimated that more than 65 million people in the United States are living with an incurable STI.[63] According to the Centers for Disease Control and Prevention (CDC), approximately 15.3 million people in the United States become infected with at least one STI annually, with nearly half of these cases occurring in people 15 to 24 years old.[64]

A number of conditions can occur as a consequence of STIs, including infertility, tubal pregnancy, cervical cancer, fetal wastage, low birthweight, congenital or perinatal infection, and other chronic conditions such as neurosyphilis. Moreover, substantial biological evidence demonstrates that a person with other STIs is more likely to both acquire and transmit HIV. Studies indicate that the more prevalent nonulcerative STIs (chlamydia infection, gonorrhea, bacterial vaginosis, and trichomoniasis) and ulcerative diseases (genital herpes, syphilis, and chancroid) increase the risk of HIV transmission by at least two to five times.[65]

NIAID supports research for more effective prevention and treatment approaches to control STIs. These approaches include (1) the development and licensure of vaccines, topical microbicides, and treatments for the microbes that cause STIs; (2) understanding the long-term health impact that sexually transmitted pathogens have in various populations; (3) stimulating basic research on the pathogenesis, immunity, and structural biology of these pathogens; and (4) developing better and more rapid diagnostics.

To carry out these activities, NIAID supports a broad STI research portfolio (*www.niaid.nih.gov/dmid/stds*) that addresses these diseases through individual investigator-initiated research grants, contracts, and a variety of research programs. Among these programs are the STI and Topical Microbicides Cooperative Research Centers, which bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. This program also supports the development of products to diagnose, treat, and prevent STIs, such as vaccines and topical microbicides. Another program, the STI Clinical Trials Group, conducts clinical trials to test safety and efficacy of interventions aimed at the prevention and control of STIs and to support clinical studies to assess the feasibility and accuracy of diagnostics and screening tests.

NIAID also supports the sequencing of the genomes of sexually transmitted pathogens, including *Chlamydia trachomatis, Neisseria gonorrhoeae, Haemophilus ducreyi, Treponema pallidum,* and *Ureaplasma urealyticum.* This information has provided new insights into the pathogenesis of numerous STIs and is paving the way for development of new diagnostics, drugs, vaccines, and microbicides.

In fiscal year (FY) 2005, NIAID continued to support and encourage the development and evaluation of STI diagnostics and other products through the Small Business Innovation Research mechanism.

Additional STI activities include the following:

- A clinical trial to compare a new oral antibiotic treatment regimen with the one currently recommended for the treatment of primary syphilis. Results from this trial could provide an alternative treatment option.

- A pivotal phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes was launched in November 2002. This clinical trial has expanded from 25 to more than 35 sites across the United States and plans to enroll 7,550 women aged 18 to 30. This study, the Herpevac Trial for Women, is being conducted as a public-private partnership with GlaxoSmithKline.

- Over the past two years, the STD Prevention Primate Unit for preclinical evaluation of topical microbicides and vaccines at the University of Washington has evaluated several candidate microbicides for safety (effects on the surface tissues and microenvironment of the cervix and vagina) in pig-tailed macaques. Results from this Division of Microbiology and Infectious Diseases-supported testing contract are being coordinated with testing conducted by the Division of Acquired Immunodeficiency Syndrome to facilitate product development and safety and efficacy testing in clinical trials.

- Five Partnerships for Topical Microbicides cooperative agreements were awarded in 2005. This program supports the development of topical microbicides with a proposed dual indication for prevention of HIV/AIDS and an STI or for two STIs. This program requires industry involvement in the partnership.

Topical Microbicides

NIAID continues to focus a great deal of its STI prevention efforts on the development of virus- and bacteria-killing gels, foams, creams, and films. These substances, known as topical microbicides, are designed to protect against sexual transmission of HIV and other STIs.

Topical microbicides work by killing HIV or other sexually transmitted pathogens or by creating a barrier that prevents them from entering or binding to cells. Ideally, microbicides would be unnoticeable, fast-acting against HIV and a broad range of other sexually transmitted pathogens, inexpensive, safe for use at least one to two times daily, and easy to store. Microbicides with and without contraceptive properties are needed so that a woman's reproductive decisions do not increase her risk for HIV/STI infection. In addition, microbicides may provide protection to men who have sex with men.

NIAID's research effort for developing topical microbicides includes basic research, preclinical product development, and clinical evaluation. The goal of this comprehensive effort is to support research and development that leads to the identification of safe and effective topical microbicides. NIAID's Strategic Plan for Topical Microbicides provides a detailed, long-range plan for advancing microbicide concepts from the laboratory to clinical trial. For more information about NIAID's Strategic Plan for Topical Microbicides, see *www.niaid.nih.gov/publications/topical_microbicide_strategic_plan.pdf*.

A number of NIAID-sponsored programs solicit for topical microbicide research. These include the Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP–HTM) and the HIV Microbicide Design and Development Teams (MDDT) program. The IPCP-HTM focuses on iterative preclinical and clinical research for novel microbicide strategies against HIV infection and has two overall goals. The first goal is to encourage advanced optimization and development of new and pioneering topical microbicide candidates and combinations. The second goal is to foster translation of new microbicides/combinations from preclinical studies to pilot clinical studies and then to advance these studies into large safety and efficacy clinical trials within the HIV Prevention Trials Network (HPTN). New awards in FY 2005 focus on development of retrocyclin-based microbicides, attachment, fusion and entry

inhibitor combinations, and the development of innovative methods to measure vaginal immunity and microbicide antiviral activity. The HIV MDDT is a milestone-driven contract program designed to streamline development of microbicide candidates, emphasizing combination products with multiple active agents. Initiation of a phase I safety trial is required within the award period. The first MDDT award was made in FY 2005 to develop a novel dendrimer-based microbicide candidate, SPL7013 (VivaGel™). Additional awards for MDDTs are expected in FY 2006, and an expansion of the program is planned for FY 2007.

NIAID has entered into an agreement with the International Partnership for Microbicides (IPM) to share information and expertise in the effort to develop a vaginal microbicide. This partnership pairs NIAID's expertise in topical microbicide discovery and early product development with IPM's capacity to design optimal microbicide formulations, manufacture clinical lots for testing, and conduct clinical trials. The relationship between NIAID and IPM will accelerate the advancement of candidate microbicides. In FY 2005, the pharmaceutical industry agreed to allow IPM to further the development of three microbicides, supported previously through NIAID's former Microbicide Development Program and the current IPCP-HTM. This agreement was made possible through NIAID's support for and participation in the IPM.

NIAID, in coordination with NIH's Office of AIDS Research, is developing a new microbicide research program to foster the translation of microbicide innovations to preclinical development. This novel milestone-driven program, called the Microbicide Innovation Program (MIP), utilizes the NIH Phased Innovation Award (R21/R33) funding mechanism, which is designed to identify innovative concepts and discoveries relevant to topical microbicides and then, through a milestone-driven, phased program of support, provide the rationale and evidence needed to determine their merit as they advance along the development path.

NIAID also supports large-scale *in vitro* screening of potential HIV transmission-blocking agents through a contract with Southern Research Institute in Frederick, Maryland. Potential microbicides from the private sector and from academic and government sources are tested in several different assays that mimic the vaginal environment to determine their ability to block HIV transmission from infected T cells to cultures of cells lining the human cervix. In FY 2005, 367 compounds were tested.

Microbicide development also is supported through a NIAID contract with the University of Washington. During the past year, several candidate microbicides were evaluated for safety (effects on the surface tissues and microenvironment of the cervix and vagina) in nonhuman primates. Results from these and other testing efforts will be coordinated to facilitate product development and safety and efficacy testing in clinical trials.

Several promising topical microbicide candidates are in various stages of clinical testing. BufferGel™ is an acid-buffering gel that helps maintain the normal acidic environment of the vagina during coitus to disrupt the transmission of acid-sensitive sexually transmitted pathogens such as HIV. Results from clinical trials conducted by the HPTN in the United States, India, Thailand, Zimbabwe, and Malawi found BufferGel™ to be safe and well-tolerated in uninfected women and men.

The HPTN studies of PRO 2000/5 gel, a synthetic compound that inhibits HIV entry into cells, were completed recently in the United States and Durban and Johannesburg, South Africa. PRO 2000/5 gel was found to be well-tolerated at different concentrations in the two groups tested—sexually active women who

were at low risk of HIV infection and sexually abstinent, asymptomatic, HIV-infected women.

NIAID is currently conducting a phase II/IIb study, called HPTN 035, to further evaluate the safety and effectiveness of these two compounds in preventing HIV infection in women. HPTN 035 is a four-arm, multisite, randomized controlled trial comparing BufferGel™ and 0.5% PRO 2000/5 Gel (P) with a placebo gel and with no treatment. Approximately 3,220 women will participate in the study. Enrollment is currently being conducted at sites in Philadelphia, Pennsylvania; Lilongwe, Malawi; and Durban and Hlabisa, South Africa. Additional sites in Blantyre, Malawi; Harare and Chitungwiza, Zimbabwe; and possibly Lusaka, Zambia, will join the trial as site preparations are successfully completed.