SEXUALLY TRANSMITTED INFECTIONS

Sexually transmitted infections (STIs), also commonly referred to as sexually transmitted diseases (STDs) are critical global and national health priorities because of their relationship with HIV/AIDS and the devastating impact they have on women and infants. In the United States, more than 65 million people are living with an incurable STI, and an estimated 15 million people become infected with at least one STI annually, approximately one-half of whom contract infections that will affect them for the rest of their lives.[48]

A number of conditions may occur later as a consequence of having 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 the presence of other STIs increases the likelihood of both transmitting and acquiring HIV. Recent 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 twofold to fivefold *(www.thebody.com/sfaf/autumn00/std.html#synergy).*

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),* which addresses these diseases through individual investigator-initiated research grants, contracts, and a variety of research programs. Among these programs are the STD Cooperative Research Centers (CRCs), 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, which is currently being recompeted, has been broadened to include topical microbicides. Another program, the STD Clinical Trials Unit, conducts clinical trials to test the safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of STIs. The Topical Microbicides Program conducts basic research, product development, and clinical evaluation activities aimed at developing female-controlled barrier methods for the prevention of HIV/AIDS and other STIs.

NIAID also supports the sequencing of the genomes of sexually transmitted pathogens, including *Chlamydia trachomatis, Neisseria gonorrhoeae*, and *Haemophilus ducreyi.* NIAID also continues to provide support for databases of genomic and postgenomic information and analysis tools on sexually transmitted pathogens *(www.stdgen.lanl.gov).* This information has provided new insights into the pathogenesis of numerous STIs and is paving the way for new opportunities to

develop diagnostics, drugs, vaccines, and microbicides.

In fiscal year 2003, NIAID continued to support and encourage the development and evaluation of STI diagnostics designed for point-of-care use through the Small Business Innovation Research mechanism. NIAID also is supporting 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.

Additional STI activities include the following:

- A pivotal phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes opened in November 2002 and will enroll 7,550 women at approximately 25 sites across the United States. This study, which is called the Herpevac Trial for Women, is being conducted as a public-private partnership with GlaxoSmithKline. The trial is estimated to require 4 years to complete.
- Over the past year, 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 surface tissues and microenvironment of the cervix and vagina) in pig-tailed macaques. Results from this Division of Microbiology and Infectious Diseases (DMID)-supported testing contract are being coordinated with testing conducted by the Division of Acquired Immunodeficiency Syndrome (DAIDS) to facilitate product development and safety and efficacy testing in clinical trials.

Topical Microbicides

NIAID continues to focus a great deal of its prevention efforts on the development of virus- and bacteria-killing gels, foams, creams, or films, known as topical microbicides, as a means of protecting 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 affect 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.

The first joint meeting of DMID, DAIDS, and National Institute of Child Health and Human Development (NICHD)-supported investigators conducting research on topical microbicides was held March 18–20, 2003. This meeting, called the Topical Microbicides Development and Evaluation Workshop, focused on issues ranging from basic research to microbicide formulation and applicator design. It provided a forum for establishing collaborations among STI and HIV

investigators involved in microbicide development.

The Microbicide Preclinical Development Program, which is sponsored jointly by NIAID and NICHD, supports the discovery and preclinical development of novel or underexplored HIV microbicides. Three awards have been made by NIAID under this program, and three by NICHD. In an effort to foster translational research, which takes promising concepts from early preclinical studies into pilot clinical studies, NICHD and NIAID jointly sponsor another program—the Integrated Preclinical/Clinical Program for HIV Topical Microbicides. Several awards have been made by NIAID and NICHD, all of which focus on iterative preclinical and clinical research for novel microbicide strategies against HIV infection. Additional awards will be made in the coming year as the Integrated Preclinical/Clinical Program for HIV Topical Microbicides continues to expand.

The Innovation Grants for AIDS Research Program stimulates new, scientifically challenging, and untested ideas in AIDS research, with a particular focus on microbicide research. NIAID made three awards under this initiative to (1) examine a novel microbicide concept, (2) develop a new model for evaluating the efficacy of microbicides *in vivo*, and (3) examine topical virucides for preventing oral transmission of HIV.

In the past year, NIAID also issued a new request for proposals that will provide contract support to help NIAID staff identify potential new microbicide candidates and provide comprehensive support for small-scale production and packaging, preclinical testing, and documentation leading to investigational new drug (IND) submission for phase I testing of candidate microbicides. It is anticipated that an award will be made in the coming year.

NIAID 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 the past year, 38 unique compounds from outside sponsors and 191 unique compounds from the National Cancer Institute Repository were tested. Colorless or lightly colored compounds with a high therapeutic index are undergoing additional evaluation to assess their potential for development as topical microbicides, to determine whether they cause intravaginal irritation or other adverse effects in experimental animals, and to determine whether they remain stable in the vagina after delivery. Promising compounds will be moved forward in the development pipeline on the basis of specific criteria.

In addition, a new assay was developed through this contract to monitor the ability of a compound to block entry of HIV into cells that carry a particular co-receptor protein on their surfaces called CCR5. A new database also was developed to maintain detailed information about tested compounds, including details of the assays performed and the results. To date, a total of 210 of the new assays have been performed.

Microbicide development also is supported through a 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 through NIAID's HIV Prevention Trials Network (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 works by inhibiting HIV entry, were completed recently in the United States and Durban and Johannesburg, South Africa, among sexually active women who were at low risk of HIV infection and in sexually abstinent asymptomatic HIV-infected women. PRO 2000/5 gel was found to be well tolerated at different concentrations.

Now that studies of PRO 2000/5 gel and BufferGel® have shown that they are both safe and well tolerated, NIAID is planning a phase II/IIb study, called HPTN 035, to further evaluate the safety and effectiveness of these compounds in preventing HIV infection in women. Toward that end, a study was conducted in HIV-infected men to determine the acceptability of both products because it is likely that men will be exposed to these products in the course of the phase II/IIb trial. The results indicated that BufferGel® and PRO 2000/5 gel are both relatively safe in that population. An external scientific review panel of outside experts was convened in May 2003 to review the planned trial and confirmed the trial's merit.

To further prepare for the implementation of HPTN 035, an HIV prevention preparedness study also has been initiated at four international HPTN sites in Zambia, South Africa, and Tanzania. This study will assess the ability of sites to recruit and retain participants for future efficacy trials of topical microbicides and to develop reliable data on HIV seroprevalence and seroincidence in the target populations.

Several phase I studies of new products also have been initiated within HPTN. These include studies of 6-percent cellulose sulfate gel, an HIV entry blocker; 9-(2-phosphonylmethoxypropyl)-adenine (PMPA), which inhibits HIV replication; and 0.5 percent PRO 2000/5 gel (P) among female participants and their partners and among sexually active uninfected women at both low and high risk for HIV infection. PMPA gel prevented the infection of female monkeys with simian immunodeficiency virus (SIV), a relative of HIV, when they were exposed to SIV in the vagina. The phase I study will determine the safety and acceptability of PMPA gel for vaginal use among sexually abstinent and active HIV-uninfected and HIV-infected women and their male sexual partners, when relevant. The phase I study of cellulose sulfate will be conducted in collaboration with the CONRAD Global

Microbicide Project and also will examine the safety and acceptability of the gel among HIV-infected women and their male sexual partners, when relevant.

A strategic plan detailing NIAID long-range plans for the whole spectrum of microbicide research, from laboratory to clinical trials, was completed and will be available in printed form and on NIAID's Web site.