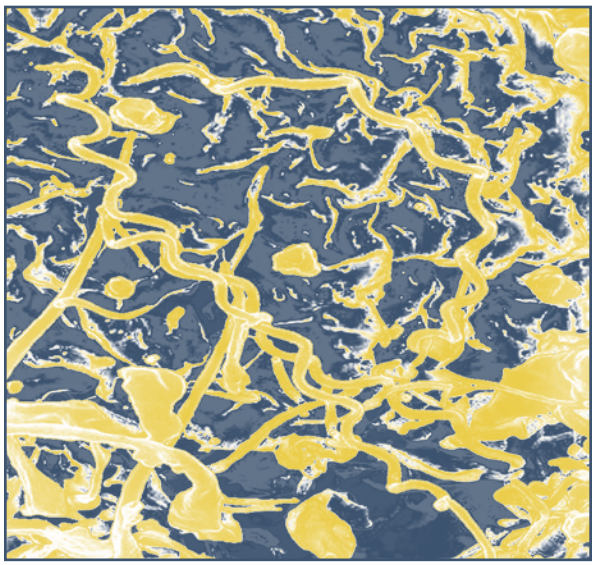
SEXUALLY TRANSMITTED INFECTIONS

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.[60]

A number of conditions can 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.[61]

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, 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.



***Treponema pallidum,* the organism that causes syphilis.**

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 2004, 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. Launched in November 2002, this clinical trial has expanded from 25 sites to 35 sites across the United States and plans to enroll 7,550 women between the ages of 18 to 30. 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 2 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 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 to facilitate product development and safety and efficacy testing in clinical trials.
- The STD Clinical Trials Unit has completed a multisite clinical study to determine the concordance of trichomoniasis between male and female partners. A manuscript for publication of data is being written.
- A protocol has been developed to conduct a three-site trial in Madagascar testing the effectiveness of the diaphragm to prevent chlamydia and gonococcal infection in women. The study is scheduled to begin in early 2005.
- The Sexually Transmitted Infections Clinical Trials Group (STI CTG) was awarded two new contracts in September 2004. The STI CTG will provide an infrastructure to conduct clinical trials to test the safety and efficacy of interventions aimed at the prevention or control of STIs and to support clinical studies to assess the feasibility and accuracy of diagnostic and screening tests.

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. NIAID's Strategic Plan for Topical Microbicides, a document that provides a detailed, long-range plan for advancing microbicide concepts from the laboratory to clinical trial evaluation was officially released this past year and can be found at: *www.niaid.nih.gov/publications/topical_microbicide_strategic_plan.pdf*.

A number of NIAID-sponsored programs solicit for topical microbicide research. These include the Innovation Grants for AIDS Research Program, the Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP–HTM) and the HIV Microbicide Design and Development Team. The Innovation Grant Program stimulates new, scientifically challenging, and untested ideas in AIDS research, with a particular focus on microbicide research. The IPCP-HTM focuses on iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The overall goal is to encourage advanced optimization and development of new and pioneering topical microbicide candidates and combinations and to foster translation of new microbicides/combinations from preclinical studies to pilot clinical studies in order to segue these studies into large safety and efficacy clinical trials within the HIV Prevention Trials Network. These new awards significantly expand the scope of the IPCP-HTM to introduce programs focusing on development of combination inhibitors using dendrimer platform technology, rectal microbicide development, and delivery strategies using engineered *Lactobacilli*. The HIV Microbicide Design and Development Teams 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 of these contracts will be awarded in 2005.

This past year, NIAID awarded a Master Contract for Preclinical Development to help identify potential new microbicide candidates and provide all support needed for small-scale production and packaging, preclinical testing, and documentation leading to Investigational New Drug submission for phase I clinical testing.

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, 345 compounds were tested.

Microbicide development also is supported through a DMID 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. 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. This study is currently enrolling patients.

This past year, three phase I clinical trials of topical microbicide candidates were completed. They were A Phase I Safety and Acceptability Study of the Investigational Vaginal Microbicide PRO2000/5 Gel (P) (HPTN 047); A Phase I Safety and Acceptability Study of the Vaginal Microbicide 6% Cellulose Sulfate Gel Among HIV-Infected Women (HPTN 049); and A Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel (HPTN 050). In all three trials, the products were found to be safe and acceptable by participants as well as their sexual partners (where relevant).