Women's Health in the U.S.

Research on Health Issues Affecting Women

National Institute of Allergy and Infectious Diseases

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Executive Summary

A number of diseases affect women at a disproportionately high rate. Many of these are infectious, immunologic, and allergic diseases that fall under the mandate of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The Institute conducts research, either through its own laboratories or through funded mechanisms, on a broad spectrum of these diseases. Virtually all of NIAID's clinical studies on the treatment and prevention of human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS), autoimmune diseases, chronic fatigue syndrome, and sexually transmitted infectious (STIs) involve women.

Rates of HIV/AIDS continue to rise among women worldwide. By the end of 2002, the Joint United Nations Programme on HIV/AIDS estimated that nearly 50 percent (19.2 million) of all adults living with AIDS worldwide were women.[1] In the United States, women accounted for approximately 32 percent of the 35,147 reported cases of HIV infection and 26 percent of the 43,950 reported cases of AIDS among adults and adolescents in 2002.[2]

NIAID researchers are conducting numerous studies of HIV and women, including studies to shed light on how women acquire HIV. These studies have shown that many factors—including viral load, STIs, alcohol use, crack or cocaine use, history of childhood sexual abuse, and current domestic abuse—are associated with increased risk of heterosexual transmission of HIV.

Mother-to-infant transmission of HIV—which can occur during pregnancy or childbirth or through breastfeeding—accounts for more than 90 percent of all cases of childhood HIV infection, especially in countries where effective antiretroviral therapies are not widely available.

According to the Centers for Medicare & Medicaid Services (www.cms.gov/hiv), of the 18 million women in the United States eligible for Medicaid, approximately 32,000 are infected with HIV; of those, about 3,000 are pregnant. Virtually all new infections in children are transmitted perinatally. Needless to say, as more women of childbearing age become infected, the number of children infected with HIV also is expected to rise. Several NIAID-funded clinical research networks are examining various treatment regimens and prevention strategies.

NIAID also has taken the lead on another health issue for women—autoimmune diseases, which include systemic lupus erythematosus (SLE), rheumatoid arthritis, and multiple sclerosis. Although many autoimmune diseases are rare, collectively these chronic diseases afflict 5 to 8 percent of the U.S. population and disproportionately affect women. Specifically, 90 percent of the nearly 2 million Americans diagnosed with (or suspected of having) SLE are women. SLE damages multiple tissues and organs and may affect muscles, skin, joints, and kidneys, as well as the brain and nerves.

The Institute also conducts research on a debilitating condition, chronic fatigue syndrome (CFS), a disorder that is diagnosed 2 to 4 times more often in women than in men. NIAID and the National Institute of Nursing Research are co-sponsoring a large-scale clinical trial of cognitive behavioral therapy and graded exercise in patients with CFS. NIAID also continues to support three CFS Cooperative Research Centers.

An estimated 15 million new cases of STI occur in the United States each year. Although some STIs (e.g., syphilis) have declined in women, others (e.g., genital herpes, gonorrhea, chlamydia) continue to spread through the population, posing a significant public health problem. Because symptoms in women are minor or nonspecific, especially in the early stages, STIs in women sometimes are not diagnosed until late in the disease. STIs that occur during pregnancy also can affect the fetus or newborn. About one-quarter to one-half of women infected with an STI during pregnancy give birth to either premature or low-birthweight infants. In about one-third to two-thirds of these pregnancies, the infection is passed to the infant, possibly causing permanent disabilities. Chlamydia, gonorrhea, and other infections of a woman's upper reproductive tract also can complicate pregnancy.

NIAID's multidisciplinary research strategy to address the complications of STIs includes basic science, vaccine development, behavioral science, development of topical microbicides, and development of rapid and inexpensive diagnostic tests. Because research increasingly connects the risk of HIV transmission to the presence of STIs, NIAID continues research into the biological, biochemical, and behavioral basis of various STIs, as well as their manifestations and potential treatments. NIAID supports STI research through grants to individual investigators, a variety of research programs, the Sexually Transmitted Disease (STD) Cooperative Research Centers, the Institute's STD Clinical Trials Unit, and NIAID's Topical Microbicides Program Projects.

An estimated 3 million new infections of *Chlamydia trachomatis* occur each year. Investigators at NIAID's Rocky Mountain Laboratories are studying the immune response to chlamydial infection and conducting preclinical testing of candidate vaccines. With frequent noninvasive urine-based screening, NIAID scientists have determined that 24 percent of high-risk youths are infected with chlamydia, and more than 15 percent become reinfected within a 6-month period.

About one in five adults in the United States has genital herpes, but only one-third of those people are aware that they have the virus. Although most genital herpes cases present no symptoms, asymptomatic individuals can transmit herpes simplex virus (HSV) to others, and a pregnant woman infected with HSV can transmit the virus to her baby. Between 20 percent and 60 percent of U.S. women of childbearing age have been infected with genital herpes,[3] posing a significant risk of neonatal herpes. NIAID is currently investigating prevention methods, including antiviral drugs, monoclonal antibodies, and vaccines. Because 45 to 60 million people in this country have genital herpes, these studies are important in assessing the role of antiviral suppressive therapy in decreasing herpes transmission. The evaluation of monoclonal antibodies as part of a concomitant therapeutic regimen for babies with neonatal HSV infection also could help battle the persistent problem of neonatal herpes, which is still a life-threatening infection despite the availability of antiviral therapies. NIAID researchers are focusing on two major viral processes in their efforts to discover new targets for anti-HSV therapies: viral binding and entry into the host cell and viral DNA replication. NIAID scientists also are investigating how the virus enters living cells and how it replicates itself. Answers to these questions will help researchers to discover new targets for anti-HSV therapies.

NIAID continues to support a comprehensive program of research on gonococcal infection. An infected pregnant woman may transmit gonorrhea to her infant during childbirth; this can result in gonococcal infection of the baby's eyes, throat, or respiratory tract. A high priority for NIAID is to develop tools to prevent gonorrhea and to gain new insights into the disease's pathogenesis, paving the way for opportunities for new diagnostic, drug, vaccine, and microbicide developments.

At any one time, an estimated 20 million people in the United States have genital human papillomavirus (HPV) infections that can be transmitted to others. Studies show high levels of HPV infection in women, with highest levels in the younger age groups. NIAID-supported scientists are investigating several promising new therapies for HPV.

Although sexual activity is the most common way to transmit syphilis, pregnant women with the disease can pass the bacterium to their unborn children, possibly causing mental and physical problems for the children. NIAID currently is supporting a clinical research protocol examining a single oral dose of therapy for early syphilis. The Institute's research program on syphilis supports the Public Health Service's effort to eliminate the infection in the United States by 2005.

NIAID's research to develop topical microbicides to kill STI pathogens, including HIV, includes basic research, preclinical product development, and clinical evaluation. The Institute supports six Topical Microbicide Program Projects and recently initiated the Microbicide Preclinical Development Program. NIAID also sponsors Topical Microbicide Preclinical Workshops to assess the state of current knowledge about preclinical methods and microbicide candidates for preventing the sexual transmission of bacteria, protozoa, and viruses, including HIV.

NIAID's commitment to basic and applied research is supported through its initiatives to enroll women in clinical research, including biomedical and behavioral

studies. The Institute fully complies with the 1993 NIH *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research,* which stipulate that women and members of minority groups must be included in all NIH-supported research projects involving human subjects (unless there is a compelling reason that such inclusion would be inappropriate). The guidelines also state that women of childbearing potential should not be routinely excluded from participation in clinical research.

In addition to funding research, NIAID collaborates extensively with other NIH Institutes and Centers, as well as with private organizations. The Institute supports and co-sponsors conferences, meetings, and workshops. The Institute communicates not only research results to scientists through workshops and conferences, but also medical information to the public and to physicians through its Office of Communications and Public Liaison. Every year, approximately 12,000 people call NIAID for information, and thousands more write for copies of pamphlets and other materials.

Acquired Immunodeficiency Syndrome

First reported in the United States in 1981, acquired immunodeficiency syndrome (AIDS) is caused by human immunodeficiency virus (HIV), which destroys CD4+ T lymphocytes that are critical in immune system functioning. This loss of CD4+ T cells impairs the body's ability to fight off infections and certain cancers.

HIV is spread most commonly during sexual intercourse with an infected partner. Several factors put women at risk of acquiring HIV, including substantial mucosal exposure to seminal fluids, prevalence of nonconsensual sex, sex without condom use, and unknown risk behaviors of sexual partners. HIV also can be transmitted by contact with infected blood, most often by sharing needles or syringes. In the United States, the risk of acquiring HIV from blood transfusions is now extremely small because all blood products in this country are screened routinely for evidence of HIV. In addition, the virus can be transmitted from pregnant women to their offspring during pregnancy, birth, or breastfeeding. Although the availability and use of effective antiretroviral therapies has dramatically reduced mother-to-infant transmission of HIV in the United States, this type of transmission continues to contribute to the escalating number of people suffering from HIV and AIDS on a global scale.

Worldwide, the number of women infected with HIV is increasing. As of December 2002, the UNAIDS/World Health Organization (WHO) reported that 19.2 million women were living with HIV/AIDS worldwide, accounting for 50 percent of the nearly 39 million adults with HIV/AIDS. In 2002, women accounted for 32 percent of the 35,147 reported cases of HIV infection in adults and 26 percent of all reported cases of AIDS in the United States. The incidence of AIDS continues to increase among U.S. women at a disproportionately high rate compared with men. From 1999 through 2002, the number of AIDS diagnoses increased 7 percent among women and decreased 5 percent among men.

Minority women also are affected by HIV/AIDS at a disproportionately high rate. In the United States, African Americans and Hispanic Americans accounted for 79 percent of all adult and adolescent women living with AIDS by the end of 2002.

Women suffer from many of the same complications of HIV/AIDS that afflict men. They also may develop complications that are different from those of men, such as recurrent vaginal yeast infections, pelvic inflammatory disease, genital ulcer disease, severe herpes infections, gender-specific abnormalities related to infection with human papillomavirus, and carcinomas of the vulva and vagina. In addition, while women experience many of the same complications of antiretroviral therapy as men, such as metabolic abnormalities like lipodystrophy and fat redistribution, they often exhibit different characteristics of these adverse effects, compared with men.

Transmission of HIV to Women

WHO estimates that more than 80 percent of adult HIV infections worldwide are due to heterosexual transmission; this mode is also the main source of infection for women in the United States. In 2002, of the adult and adolescent U.S. women living with AIDS, 72 percent had been infected through heterosexual contact with HIV-infected men and 26 percent through injection drug use.

In the United States, studies have shown that during unprotected heterosexual intercourse with an HIV-infected partner, women have a greater risk of becoming infected than do men. In other parts of the world, however, this is not necessarily true, possibly because of the lack of circumcision in men. NIAID-funded studies are under way to determine whether circumcision of adult men can reduce the risk of HIV acquisition through sexual transmission.

Other important findings about the transmission of HIV to women are emerging from studies by the HIV Prevention Trials Network (HPTN), a global network established to develop and evaluate nonvaccine prevention interventions. HPTN is funded by NIAID and the National Institute of Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA), and the National Institute of

Mental Health. A previous HPTN study found that among heterosexual couples in which one individual was HIV positive and the other uninfected, viral load is the main predictor of risk of heterosexual HIV transmission. The study also showed that transmission is rare among persons with viral loads below 1,500 copies of HIV-1 RNA per mL. The challenge facing researchers is to use this information to develop prevention strategies that will slow the continued spread of HIV. Studies currently are being planned to evaluate whether reducing viral load also can reduce the risk of sexual transmission of HIV.

Studies both in the United States and abroad have demonstrated that sexually transmitted infections (STIs), particularly infections that cause ulcerations of the vagina (e.g., genital herpes, syphilis, chancroid), greatly increase a woman's risk of HIV infection. NIAID-funded cohort studies in the United States also found a number of other factors associated with increased risk of heterosexual transmission of HIV, including alcohol use, history of childhood sexual abuse, current domestic abuse, and use of crack or cocaine.

Prevention of HIV Transmission

NIAID continues to focus a great deal of its prevention efforts on the development of topical microbicides, such as virus- and bacteria-killing gels, foams, creams, or films, 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 and blocking the pathogens' ability to enter or bind with 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 are needed both with and without contraceptive properties 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 safe and effective topical microbicides includes basic research, preclinical product development, and clinical evaluation. (See "Topical Microbicides" on page 22.)

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

In the past year (fiscal year [FY] 2003), NIAID also issued a new request for proposals that will provide contract support to help NIAID staff identify potential new microbicide candidates. Contract support also will include all the assistance needed for small-scale production and packaging, preclinical testing, and documentation leading to investigational new drug submission for phase I testing of candidate microbicides. It is anticipated that an award will be made in FY 2004.

In addition, a new assay was developed through another contract to monitor the ability of a potential new microbicide to block entry of HIV into cells that have a particular co-receptor, CCR5. A new database also was developed to maintain detailed information about the compounds, the assays performed, and the results of screenings with this new assay. To date, a total of 210 new assays have been performed.

During the past year, several candidate microbicides were evaluated in nonhuman primates for safety (effects on the surface tissues and microenvironment of the cervix and vagina) through a contract with the University of Washington. 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 HPTN in the United States, India, Thailand, Zimbabwe, and Malawi found BufferGel® to be safe and well tolerated in uninfected women and men.

In May 2003, an External Scientific Review Panel of outside experts was convened to review a proposed

phase II/IIb safety and efficacy study of BufferGel® and 0.5 percent PRO 2000/5 Gel (P), another topical microbicide, in preventing HIV infection in women. The Panel's recommendations confirmed the merit of the trial, which will be called HPTN 035.

In preparing for the implementation of HPTN 035, an HIV-prevention preparedness study has been initiated at multiple international HPTN sites in Zambia, South Africa, and Tanzania. The purpose of the preparedness study is to 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 microbicide products also have been initiated within HPTN. Products being studied include a 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), which will be studied among female participants and their partners and among sexually active uninfected women at low and higher risk for HIV infection. The phase I study of the cellulose sulfate gel will be conducted in collaboration with the Contraceptive Research and Development Program (CONRAD) Global Microbicide Project. The study will examine the safety and acceptability of the gel among sexually abstinent and active HIV-infected women and, when relevant, their male sexual partners.

In earlier studies, PMPA gel prevented infection in female monkeys when they were exposed to simian immunodeficiency virus, a relative of HIV, in the vagina. The new phase I study of PMPA gel will determine its safety and acceptability for vaginal use among sexually abstinent and active women, with and without HIV infection, and their male sexual partners.

Previous studies of PRO 2000/5 Gel showed it to be safe and well tolerated as a vaginal gel in women who are not sexually active. The new phase I study examined the safety and acceptability of the gel among sexually active HIV-uninfected and sexually abstinent HIV-infected women.

A strategic plan detailing NIAID long-range plans for the whole spectrum of microbicide research, from laboratory to clinical trials, was completed and is available in printed form and on NIAID's Web site at www.niaid.nih.gov/publications/topical_microbicide_strategic_plan.pdf.

Natural History and Epidemiologic Research

The Women's Interagency HIV Study (WIHS), established in 1997, is a multicenter, longitudinal study designed to examine the natural history of HIV infection in U.S. women. The study is co-sponsored by NIAID, NICHD, NIDA, the National Cancer Institute, and the National Institute of Dental and Craniofacial Research.

WIHS operates in tandem with the HIV Epidemiology Research Study, funded by the Centers for Disease Control and Prevention. In recent years, the study was expanded so that it could better examine the natural history of HIV among women in an era of combination treatments referred to as highly active antiretroviral therapy (HAART). This expansion is enabling researchers to evaluate clinical outcomes in the context of HAART, time for AIDS development, impact of other infections (e.g., hepatitis C virus), treatment and its effects in women, impact of aging on HIV, and impact of hormonal factors on HIV. WIHS also supports research on HIV pathogenesis, including HIV virology, HIV resistance to antiretroviral drugs, illicit drug use and HIV resistance to antiretroviral therapies, human papillomavirus infection, and associated cervical and anal cancers.

In the past, WIHS researchers examined factors associated with an increased risk of HIV transmission and the impact of HAART. These studies showed that HIV infection and the use of antiretroviral therapy were not associated with changes in menstrual cycle. Recently, however, WIHS investigators examined menstrual cycles and how substance abuse, psychotherapeutic medications, alcohol or tobacco consumption, and the use of marijuana or crack cocaine were or were not associated with menstrual irregularities. Only the use of psychotherapeutic medications was found to affect the odds of having either a very short or a very long cycle. These findings emphasize the need for clinicians to take into consideration any use of non-HIV-related

medications and lifestyle factors when evaluating menstrual disruptions in HIV-infected women.

Another WIHS study published this year found that the incidence of diabetes mellitus was significantly higher among HIV-infected women who used protease inhibitors compared with women receiving reverse transcriptase inhibitors, women not on any antiretroviral therapy, and uninfected women. These results suggest that routine diabetes screening should be considered, especially among heavier and older women who are using protease inhibitors and who are from populations already at an increased risk of diabetes.

Previous research has shown that high levels of C-reactive protein, an inflammatory marker, predict a poorer prognosis for other diseases, including atherosclerosis, renal disease, and cancer. Building on these findings, WIHS researchers also conducted a study of 204 HIV-infected women to determine whether C-reactive protein might serve as a low-cost way to help evaluate HIV disease progression in women. The researchers found that higher C-reactive protein levels were associated with a higher risk of death in this population of HIV-infected women, suggesting that C-reactive protein levels may be a useful and inexpensive predictor of HIV disease mortality in women.

Treatment Research in HIV-Infected Women

Data from WIHS and other studies, in combination with basic research, provide the foundation for studying therapeutic interventions. Several NIAID-funded clinical research networks—the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)—conduct studies of various treatment regimens for HIV/AIDS, as well as the complications and co-infections associated with HIV. In addition, NIAID intramural scientists conduct clinical studies at the NIH Clinical Center. All these clinical trial networks identify and evaluate different strategies for treating women and their infants and for preventing perinatal transmission. Each network is committed to ensuring the inclusion of HIV-infected women in clinical trials and conducting research on HIV-associated conditions that affect both pregnant and nonpregnant women. These programs are committed to identifying real or potential barriers to recruiting and retaining women for participation in each of these clinical trials. To address these issues directly, NIAID initiated a new program called Enrolling Women and Minorities in HIV/AIDS Research Trials, which will support projects that identify factors negatively affecting the recruitment of women and minorities. The program also will plan and develop mechanisms and interventions that will facilitate the recruitment and retention of these populations in research trials. Specifically, the program will fund innovative and practical approaches to access, enroll, and retain women and racial/ethnic minorities in HIV/AIDS research trials in the United States.

These clinical research networks test therapies to treat HIV infection, evaluate therapies to treat complications of HIV and other diseases that often accompany HIV infection, and evaluate gender-specific studies. Because HIV suppresses the immune system, the body is hampered in its ability to resist infection. Women often develop different complications than do men. For example, HIV-infected women frequently develop candidiasis, or yeast infections of the mouth, vagina, and throat. These infections are persistent and difficult to treat, often increasing in severity as the immune system weakens.

During FY 2003, 1,485 women participated in AACTG studies, 2,984 in PACTG studies, and 773 in CPCRA studies. Respectively, women accounted for 19.3 percent, 55.5 percent, and 22.0 percent of patients in studies in each of these clinical research groups.

The Women's Health Committee of AACTG, in conjunction with PACTG, has developed a scientific agenda to promote research in the area of gender- and sex-specific research in HIV/AIDS. Several research protocols are now open or in development in the following areas:

- Pharmacokinetics of contraceptives, in the setting of HAART
- Antiretroviral therapy in pregnancy: Primary therapy of HIV in pregnancy
- Gender differences in HAART responses evaluated in large naive treatment trials

- Comparison of three protease inhibitor-sparing regimens for the initial treatment of HIV infection
- Assessment of prevalence and persistence of human papillomavirus DNA in HIV-infected women who are protease-inhibitor naive and have initiated HAART
- HIV viral kinetics
- Virologic studies in compartmental samples from HIV-infected subjects changing or initiating potent antiretroviral therapy
- Changes in immunologic responses in female genital secretions
- Observational study of virologic and immunologic changes in HIV-infected women during the postpartum period
- Evaluation of metabolic complications (such as hepatic steatosis and chronic HIV infection) associated with antiretroviral medications in HIV-1-infected pregnant women

In May 2003, NIAID sponsored a workshop in conjunction with the National Heart, Lung, and Blood Institute to evaluate the status of research on cardiovascular complications of HIV disease. As a result of the workshop, new protocols are being developed in WIHS to advance our understanding of cardiovascular disease in HIV-infected women.

HIV Transmission From Mother to Infant

In the United States and other developed countries, the transmission rate of HIV from mothers to their newborn infants ranges between 15 percent and 25 percent of women who do not receive zidovudine (AZT) or a combination of antiretroviral therapies. This percentage translates to approximately 1,000 to 2,000 HIV-infected infants born each year. The risk of mother-to-infant transmission is significantly higher if the mother has advanced HIV disease, large amounts of HIV in her bloodstream, or lower than normal counts of CD4+ T cells.

In 1994, NIAID supported a clinical trial, known as ACTG 076, that demonstrated that administering AZT to HIV-infected women during pregnancy and delivery and to their babies during the first weeks of life reduced the risk of mother-to-infant HIV transmission from 25 percent to 8 percent. This study resulted in publication of *Public Health Service Guidelines on the Use of Zidovudine (AZT) to Reduce Perinatal Transmission of HIV*.

Several NIAID-funded studies are conducted through PACTG, a large clinical trials network for HIV/AIDS research in children and adolescents, and through the Women and Infants Transmission Study (WITS), a prospective cohort study that has been following HIV-infected mothers and their children since 1988. The researchers are examining factors that contribute to perinatal transmission, evaluating disease progression and contributing factors during pregnancy and postpartum in HIV-infected women and their infants, and evaluating diagnostic tools for determining HIV status in infants. Sponsored by NIAID, NICHD, and NIDA, WITS is examining cohorts in Chicago, Boston, New York, Houston, and San Juan.

In addition, HPTN evaluates a broad range of nonvaccine prevention strategies to reduce HIV transmission, including interventions for preventing mother-to-infant transmission of HIV. Recently, investigators in HPTN reported on follow-up data from a long-term NIAID-funded study that began in November 1997 in Uganda. Initial findings, released in July 1999, showed that a single oral dose of the antiretroviral drug nevirapine (NVP) given to an HIV-infected woman in labor and another to her baby within 3 days of birth reduces the transmission rate by half compared with a similar short course of AZT. The study had demonstrated that the NVP regimen was highly effective and safe for preventing transmission of HIV. Because the NVP regimen was more affordable and practical than any other regimen that had been examined to date, it could be implemented in resource-poor developing countries. The cost savings alone of using NVP in the study were substantial, approximately 70 times less than the AZT treatment.

Follow-up from that study now shows that the initial advantage gained by infants who, along with their mothers, received one dose of NVP, was sustained until they reached age 18 months, and few serious side effects were reported that were attributable to NVP. Approximately 99 percent of the women in the study

breastfed their children. After 18 months, most of the women had completed breastfeeding, with the average duration lasting 9 months. After 18 months, infants enrolled in the NVP regimen sustained a 41 percent reduction in risk for HIV infection when compared with infants taking the AZT regimen. These results were consistent with the 42-percent risk reduction for the infants who received NVP at age 6 to 8 weeks. The findings offer compelling new evidence that short-course NVP effectively and safely reduces mother-to-infant transmission of HIV. A final follow-up study will be conducted in 2004 when the children are aged 5 years.[4]

Other studies designed to evaluate strategies for reducing mother-to-infant transmission of HIV are in development or under way. One such study will examine the effect of a longer course of NVP administered to HIV-uninfected infants born to HIV-infected breastfeeding mothers. Another study will examine the benefit of passive immunization by administering HIV immune globulin (HIV-Ig) to the infant.

Immunology and Immune-Mediated Diseases

The immune system is important at all stages of life in fighting disease-causing microorganisms or pathogens, including viruses, bacteria, fungi, and parasites. The immune system also has the remarkable ability to discriminate self (its own cells) from nonself (foreign cells). A more comprehensive understanding of the immune system's role in the regulation and dysregulation of pregnancy and fertility will assist in the treatment of reproductive maladies and advance fetal, child, and maternal health. In addition, increased understanding of the mechanisms of natural maternal-fetal tolerance may allow for the development of new strategies for the induction of clinical tolerance in transplantation and autoimmune disease.

Immune-mediated diseases include a range of disorders whose basis is dysfunction of the immune system. Among them are autoimmune diseases, asthma and allergic diseases, immune-mediated graft rejection, and primary immunodeficiency disorders.

Autoimmune Diseases

More than 80 distinct autoimmune diseases have been identified. These diseases can be divided into organ-specific and nonorgan-specific diseases. Organ-specific diseases are characterized by immune reactions and tissue damage localized to a single organ or tissue. Examples include type 1 diabetes and multiple sclerosis, where the primary lesions are localized in the pancreas and the central nervous system, respectively. Nonorgan-specific diseases, such as systemic lupus erythematosus (SLE), are characterized by immune reactivity against antigens distributed throughout the body, resulting in widespread damage.

Many of the autoimmune diseases are rare. As a group, however, autoimmune diseases afflict millions of Americans. Most autoimmune diseases strike women more often than men; in particular, they affect women of working age and during their childbearing years. Because of their chronic nature and debilitating complications, autoimmune diseases can exact high medical and socioeconomic costs. Treatment strategies for autoimmune diseases are directed at restoring the normal immune response, preventing further tissue and organ injury, and limiting or preventing complications such as infection.

Although we have gained considerable understanding of the mechanisms that mediate tissue injury in autoimmune diseases, there are significant gaps in our scientific knowledge about (1) etiologic agents that initiate autoimmune diseases, (2) genetic susceptibility, (3) regulation of T cell and autoantibody production (antibodies that react to self-tissues), (4) the cells and chemical mediators of inflammation, and (5) the role of infectious agents and environmental factors.

NIAID places a high priority on research in autoimmunity and autoimmune diseases and supports a broad portfolio of basic, preclinical, and clinical research. This research is aimed at understanding the pathogenesis of autoimmune diseases, investigating new ways to modify the immune system, and applying this knowledge to the identification and evaluation of promising approaches to treat and prevent these diseases. Two decades of productive research on the immune system have resulted in a wealth of new information and increased understanding of the immune system.

These accomplishments now provide promising opportunities for major advances in the diagnosis, treatment, and prevention of autoimmune diseases.

NIH Autoimmune Diseases Coordinating Committee

NIAID chairs the NIH Autoimmune Diseases Coordinating Committee (ADCC), established in 1998 at the request of Congress. The goal of the ADCC is to increase collaboration and facilitate coordination of research among NIH Institutes and Centers, other Federal agencies, and private groups interested in these diseases. The ADCC Autoimmune Diseases Research Plan presented to Congress in 2002 can be found at www.niaid.nih.gov/dait/pdf/ADCC_Report.pdf.

Clinical Research Programs

NIAID, in collaboration with other NIH Institutes, Centers, and Divisions, supports clinical research studies and clinical trials related to autoimmune diseases. The Autoimmunity Centers of Excellence (ACEs) is a cooperative research program of integrated basic, preclinical, and clinical research. These centers conduct single-site and multisite cooperative clinical trials for new immunomodulatory interventions for autoimmune diseases and studies of mechanisms of action of these therapies. In 2003, NIAID renewed and expanded the ACEs to include nine centers.

With co-sponsorship from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International (JDRF), NIAID supports the Immune Tolerance Network (ITN). ITN is an international consortium of more than 80 investigators in the United States, Canada, and Europe dedicated to the clinical evaluation of novel, tolerance-inducing therapies for the treatment of autoimmune diseases, asthma, and allergic diseases and to prevent the rejection of transplanted organs, tissues, and cells. The goal of these therapies is to "re-educate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. ITN also conducts integrated studies on the underlying mechanisms of these approaches and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. More information about ITN is available at www.immunetolerance.org.

Through the Clinical Trials Network for Stem Cell Transplantation for Autoimmune Diseases, NIAID is developing clinical trials to assess the efficacy of hematopoietic stem cell transplantation to treat severe autoimmune diseases such as multiple sclerosis, SLE, and scleroderma. Studies of the underlying immune mechanisms of autoimmune diseases will be performed along with the clinical trials. More information about NIH clinical research studies is available at www.clinicaltrials.gov.

The Autoimmune Disease Prevention Centers conduct basic research on the development of new targets and approaches to prevent autoimmune diseases. In fiscal year 2003, the Prevention Centers supported 14 pilot projects to test innovative approaches that may lead to the development of novel targets for disease prevention or assays for biomarkers of disease progression. The Prevention Centers are co-sponsored by NIAID, NIDDK, the National Institute of Child Health and Human Development (NICHD), the NIH Office of Research on Women's Health (ORWH), and JDRF.

Genetic Studies

NIAID also supports basic research to identify the genetic causes underlying autoimmune diseases. The knowledge gained by this research may lead to improved methods to diagnose and treat patients. In 2000, NIAID joined several NIH Institutes and Centers and JDRF in supporting the International Histocompatibility Working Group (IHWG). This network comprises more than 200 laboratories in more than 70 countries that collect and share data on genes of the human leukocyte antigen (HLA) complex. IHWG is studying five diseases for which the HLA associations have been well characterized: type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthropathy. In addition, NIAID supports a project within IHWG to identify single nucleotide polymorphisms in immune response genes, which may account for increased susceptibility of certain individuals or groups to immune-mediated diseases.

Repositories and Registries

NIAID supports the Multiple Autoimmune Disease Genetics Consortium (MADGC), a repository of genetic and clinical data and materials from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This resource provides materials to advance research aimed at discovering the human immune response genes involved in autoimmunity. MADGC has enrolled more than 150 families. More information can be found at www.madgc.org.

NIAID, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the Arthritis Foundation support the North American Rheumatoid Arthritis Consortium (NARAC), a

collaborative registry and repository of clinical data and materials from families with rheumatoid arthritis. The NARAC database has enrolled 902 families, encompassing 1,522 patient visits. Data for more than half of the 902 families have been validated, including 600 affected sibling pairs. The data registry and the repository samples that are available to all investigators should facilitate the identification and characterization of genes responsible for susceptibility to rheumatoid arthritis. More information about the consortium is available at www.naracdata.org.

Programs and Initiatives

To better understand the differences in the immune responses between males and females, NIAID funded a new research initiative in 2001, Sex-Based Differences in the Immune Response. Research supported by this initiative will identify, characterize, and define sex- and gender-based differences in immune responses. Studies include basic and clinical investigation of sex differences regulated by hormonal and nonhormonal mechanisms in response to exogenous antigens, the innate and adaptive immune response, and systemic and mucosal immunity. This initiative is co-sponsored by the National Institute of Neurological Disorders and Stroke, NIAMS, ORWH, and the National Multiple Sclerosis Society.

In 2003, three research projects were assigned to NIAID under the research initiative Bench to Bedside Research on Type 1 Diabetes and its Complications, which was co-sponsored by NIDDK, the National Eye Institute, and the National Heart, Lung, and Blood Institute. These research projects will support collaborations between clinical and basic biomedical researchers and are designed to more quickly translate advances in understanding the molecular basis of type 1 diabetes and its complications into new therapies for the prevention, diagnosis, treatment, and cure of this disease. Successful "bench to bedside" collaborations may result in clinical trials of promising new therapeutic approaches.

In collaboration with NIDDK and NICHD, NIAID supported the Diabetes Prevention Trial— Type 1, a multisite cooperative clinical trial for the prevention of type 1 diabetes in first-degree relatives of patients with type 1 diabetes. This was the first large, nationwide trial of an immunomodulatory agent for the prevention of an autoimmune disease. The arm of this trial enrolling high-risk subjects ended early with no evidence that intervention with low-dose parenteral insulin prevented the development of disease. The intermediate-risk arm, which tested the effectiveness of oral insulin to prevent the development of disease, ended in 2003 with no clinically significant outcome observed.

Workshop

Although a variety of environmental factors, including infectious agents and chemicals, have been linked to the development of autoimmune diseases both in humans and in animal models, the mechanisms by which environmental factors interact with the immune system are unclear. NIAID participated in a workshop (February 4–5, 2003) to discuss recent progress in and potential future directions for research related to environmental influences on autoimmunity and autoimmune diseases. The workshop was organized in cooperation with the National Institute of Environmental Health Sciences, NIAMS, the NIH Office of Rare Diseases, ORWH, the American Autoimmune Related Disease Association, and the U.S. Environmental Protection Agency. Plenary presentations at the workshop highlighted recent studies in epidemiology of autoimmune diseases, gene-environment interactions, and immunologic effects of environmental chemicals. Small breakout sessions focused on specific topics relevant to determining the most suitable directions for future studies and collaborations, as well as on mechanisms for coordination of resources among interested researchers.

Advances in Immunology and Immune-Mediated Diseases Research

Gender-Specific T-Cell Homing and Autoimmunity. Women are more susceptible to autoimmune diseases than men, although the reason for this difference is unknown. Female sex hormones appear to play a role in this predisposition to autoimmunity, but extensive analysis of the effects of the female sex steroids on immune responses in vitro have failed to identify the mechanism(s). This project explores the hypothesis that gender-specific differences in T-cell homing, due to effects of female sex hormones on adhesion molecule

expression, contribute to increased severity of autoimmune diseases in females by modifying lymphocyte trafficking patterns. Such gender-specific trafficking differences could be important both in the induction of disease and later in the disease process. These studies may identify novel and important mechanisms contributing to the increased incidence and severity of autoimmune disease in women.

Sex Hormone Regulation of Innate Immunity. It has been hypothesized that innate immunity (epithelial cells, neutrophils, macrophages, and natural killer cells) is under male and female sex hormone control and that, in addition to conferring protection, each type of these cells is capable of initiating an adaptive immune response. This program project addresses the hypothesis by attempting to define the role of sex hormones (androgens, estrogens, and progens) in regulating the innate immune system as it functions systemically and at mucosal surfaces. Mechanisms whereby sex hormones influence phenotype, innate function, and communication between the innate and adaptive immune systems will be defined. Researchers will use peripheral blood cells from men and women, immune cells and tissues from the female reproductive tract, and cell lines to define the role of sex hormones and pathogen challenge at the cellular and molecular levels.

Sex-Based Differences in the Immune Response. It also has been hypothesized that sex hormones play a role in immune regulation and specifically in systemic lupus erythematosus. Estrogens can alter the threshold for negative selection of naive autoreactive B cells and may thus influence the development of autoimmune diseases. Researchers will examine how estrogen leads to an increase in cells of the marginal zone B-cell subset. In addition, experiments will be conducted to investigate the differences in B-cell responsiveness to estrogen in different mouse strains to understand what underlies an estrogen-mediated breakdown in humoral self-tolerance.

The Severity of the Autoimmune Disease Lupus Correlates With the Activity of Particular Genes. SLE is a serious, relapsing, systemic autoimmune disease. NIAID-supported investigators have measured the products of more than 12,000 genes and have studied the reasons why only 33 of these genes are elevated during periods of active lupus. The products of nearly all 33 genes also are increased by the signaling proteins, called interferons, or during the maturation of a particular type of white blood cell. These results suggest that these pathways may play a central role in lupus. Moreover, a standard treatment for flare-ups of lupus disease also reduces the products of the interferon-stimulated genes, further supporting a role for interferons in lupus. These findings suggest that lupus has a relatively simple "signature" of gene activity, which may provide a much-needed objective measure of disease activity (biomarker). The findings also may identify the causes of the disease and lead to new treatment approaches.

The Female Hormone Prolactin Affects Development of Cells Involved in SLE. SLE is much more prevalent in women than in men. Scientists have long thought that female sex hormones are at least partly responsible for the increased frequency of SLE in women, but the exact role of the hormones has been unclear. An NIAID-supported research team has shown that one of these female hormones, prolactin, can influence the development of cells that produce antibodies responsible for symptoms of SLE. Treating mice susceptible to SLE with prolactin allows the survival of antibody-producing cells that are normally eliminated by the immune system and eliminates SLE symptoms. Understanding how prolactin and related hormones influence the survival and function of these cells and other components of the immune system may lead to new treatments for SLE and other autoimmune diseases.

Chronic Fatigue Syndrome

People with chronic fatigue syndrome (CFS) can suffer for years from debilitating fatigue, with unrefreshing sleep, muscle and joint aches, tender lymph glands, and a host of other symptoms, including problems with mental concentration and memory. Analgesics, antidepressants, and other symptom-based therapies can provide some relief, but no known specific treatments exist for CFS. Moreover, the search for treatments is complicated by the fact that the cause of the disease is unknown. CFS is diagnosed 2 to 4 times more often in women than in men. The onset of the syndrome may follow infection, stress, or trauma, which have been postulated to cause uncharacterized irregularities in the immune system, the nervous system, or the endocrine system. Early research endeavors focused on a hypothesized infectious cause. To date, no infectious or other cause has been reproducibly associated with CFS.

Prevalence and incidence rates for chronic fatigue syndrome have been difficult to obtain for several reasons, including lack of objectively verifiable diagnostic criteria, differences in case definitions used by different investigators, and potential biases related to case ascertainment. Given these factors, a large number of published studies have reported a wide range of prevalence estimates. The following data, collected by the Centers for Disease Control and Prevention (CDC) from 1988 to 2001, represent surveillance-derived estimates of CFS in Wichita, Kansas. These data are available at www.cdc.gov/ncidod/diseases/cfs/program-updates/cfs-uptdate-031703.htm.

- Weighted point prevalence at baseline was 235 per 100,000.
- Prevalence was elevated among women and highest among nonwhite women.
- CFS was rare in adolescents aged 12 to 17 years.

One of the first community-based investigations designed to ascertain CFS prevalence was conducted in Seattle. The individuals surveyed were members of a large health maintenance organization. These data are similar to CDC's more recent data mentioned above.

In 2000, NIAID and the Department of Health and Human Services CFS Coordinating Committee held state-of-the-science workshops to evaluate the current state of CFS research and to identify promising new areas for scientific exploration. Areas addressed at these meetings included sleep disorders, neuroendocrinology, pain, cognitive disturbance, neurally mediated hypotension, immunology, and functional disability. In response to these workshops, the trans-NIH CFS Working Group, of which NIAID is a member, issued a new Program Announcement in 2001 to stimulate further research on the pathophysiology and treatment of CFS.

In 2003, NIAID and the trans-NIH CFS Working Group sponsored a conference titled Neuro-Immune Mechanisms and CFS. The purpose of the conference was to assess the current state of the art in CFS, identify scientific gaps, and stimulate cross-disciplinary collaboration. The conference brought together CFS researchers and other established investigators in a variety of allied fields, including neuroendocrinology, neuroimaging, cognitive sciences, and sleep regulation.

NIAID, along with the National Institute of Nursing Research, is co-sponsoring a large-scale clinical trial of cognitive behavioral therapy and graded exercise in CFS patients. This study may provide important new information about response to treatment as well as individual host factors that may influence response in CFS.

NIAID continues to support three CFS Cooperative Research Centers. These centers conduct broadly focused basic, clinical, and epidemiologic research. Some highlights from these Centers are described below.

- The New Jersey CFS Cooperative Research Center is attempting to characterize heart and nervous system abnormalities in persons with CFS. In the past 2 years, researchers have analyzed the cerebrospinal fluid of 30 patients; 9 had elevated protein levels. The study also is accruing data to determine whether persons with CFS have reduced cerebral blood flow.

- The University of Washington CFS Cooperative Research Center continues to examine CFS in identical and fraternal twins, one of whom has CFS while the other does not. This research also involves gathering other information from family members. Preliminary analyses show no differences in any of the criteria studied, with the exception of some differences in T-cell activation. However, twin pairs (including healthy twins without CFS) have demonstrated remarkably disrupted sleep, poor performance on cognition tests, and impaired exercise capacity. These findings are consistent with a neurohormonal basis for CFS. The researchers continue to follow the patients enrolled in the study's clinical database.

- The University of Miami CFS Cooperative Research Center focuses on cognitive behavioral therapy for stress management in persons with CFS. Research emphasizes the importance to patients of managing symptoms even when their causes are unknown. So far, more than 30 patients are enrolled in 3 cohorts, with plans to continue enrolling new cohorts every 3 months. In the past year, screening (and referral if indicated) has been undertaken for both posttraumatic stress disorder and suicide intention. Initial findings of the research show decreased natural killer cell activity in CFS patients.

Sexually Transmitted Infections

Sexually transmitted infections (STIs) are caused by microorganisms, or microbes, particularly bacteria and viruses. A crucial difference between these two types of microbes is that bacteria are one-celled organisms that can reproduce themselves, whereas viruses are extremely small organisms consisting of genetic material surrounded by a protein shell that must reproduce within host cells, using the cells' protein-producing machinery. STIs caused by bacteria include gonorrhea, syphilis, and chlamydial infection. STIs caused by viruses include AIDS, genital herpes, genital warts, and human papillomavirus (HPV), a virus that can cause cervical cancer.

The latest estimates indicate that 15 million new cases of STIs occur in the United States each year, with approximately one-fourth of these new infections affecting teenagers. Although some STIs (e.g., syphilis) continue to decline for women, others (e.g., genital herpes, gonorrhea, chlamydia) continue to spread through the population, posing a significant public health problem.

Most of the time, STIs cause no symptoms, particularly in women. When and if they develop, symptoms often are minor or nonspecific, particularly in the early stages of an STI. They may be confused with symptoms of other diseases not transmitted through sexual contact. As a result, STIs in women sometimes are not diagnosed until late in the disease when serious problems may have developed, such as pelvic inflammatory disease (PID), which can cause infertility, and tubal pregnancy (pregnancy that occurs in the fallopian tubes rather than in the uterus).

STIs in pregnant women also can result in adverse effects to the fetus or newborn. For example, death of the fetus may occur in as many as one-quarter to one-half of women infected with syphilis. Another one-quarter to one-half of women infected with syphilis during pregnancy give birth to either premature or low-birthweight infants. Of these births, between 40 to 70 percent of the women will pass the infection to the infant, putting the infant at increased risk for permanent disabilities, such as deafness. Similarly, infants who contract congenital herpes simplex virus (HSV) from their mothers are at increased risk of microcephaly (abnormally small head).

Among both women and men co-infected with an STI and HIV, there is a markedly increased risk of transmitting HIV to others. HIV infection also may affect the natural history of STIs: diseases may progress more rapidly or be more difficult to treat. Through these interactions, STIs and AIDS amplify each other, leading to the increased prevalence of these diseases among certain populations.

NIAID's research program on STIs has four major goals:

- To develop and license vaccines, topical microbicides, and treatments for the microbes that cause these STIs;
- To understand the long-term health impact that sexually transmitted pathogens have in various populations;
- To stimulate basic research on the pathogenesis, immunity, and structural biology of these pathogens; and
- To develop better and more rapid diagnostics.

NIAID supports research through grants initiated by individual investigators and through a variety of research programs. For example, the Sexually Transmitted Diseases (STD) Cooperative Research Centers were created to bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. Another program, the STD Clinical Trials Unit, conducts clinical trials to test the safety and efficacy of biomedical and behavioral interventions aimed at prevention and control. Finally, the Topical Microbicides Program Projects conduct basic research, product development, and clinical evaluation activities aimed at the development of female-controlled barrier methods to prevent STIs and HIV infection.

Knowledge of the genetic composition of STI pathogens can provide insights into the mechanisms by which these pathogens cause disease and can help identify new vaccine candidates. Therefore, NIAID

supports research to map the genes of these organisms and to determine the sequence of the molecular building blocks, or nucleotides, that make up these genes. Researchers recently have sequenced the genomes of several sexually transmitted pathogens, including *Chlamydia trachomatis, Treponema pallidum, Ureaplasma urealyticum, Neisseria gonorrhoeae,* and *Haemophilis ducreyi*. These genome sequences have provided new insights into the pathogenesis of these diseases, paving the way for new opportunities for diagnostic, drug, vaccine, and microbicide development.

Chlamydial Infection

C. trachomatis, a bacterial pathogen, is a major cause of preventable blindness and STIs in the developing world. An estimated 3 million new infections occur each year. Moreover, cross-sectional studies and data collected from adolescent and family planning clinics have documented that adolescents aged 15 to 19 years have the highest rates of chlamydial infections, irrespective of socioeconomic status.[3]

Chlamydial infection causes most of the same syndromes and symptoms as gonorrhea (e.g., painful urination, increased vaginal discharge, abdominal pain, abnormal menstrual bleeding), although the proportion of cases with no overt symptoms is higher for chlamydial infection. Furthermore, when symptoms of chlamydia do occur, they tend to be less severe. Both chlamydia and gonorrhea can cause urethritis (inflammation of the urethra), which can result in frequent and painful urination and the presence of white blood cells in the urine. Both diseases also can produce inflammation of different parts of the female reproductive system—including the cervix, endometrium (inner membrane) of the uterus, and fallopian tubes—leading to PID. PID symptoms include vaginal discharge, pain in the lower abdomen, pain with sexual intercourse, and abnormal uterine bleeding. Recurrent or severe PID that causes fallopian tube inflammation or scarring, although sometimes "silent" or undetected, can result in infertility or tubal pregnancy.

Researchers have learned that the mouse model of *C. trachomatis* infection mimics human infection and is therefore useful for studying the immune response to chlamydial infection and for preclinical testing of candidate vaccines. Investigators at NIAID's Rocky Mountain Laboratories are using this model to learn what constitutes a protective immune response in the genital mucosal and to determine what chlamydial component is necessary to elicit this response. These studies will be useful in formulating vaccines for the prevention of chlamydial STI in humans.

A major problem with controlling chlamydia is the fact that more than 80 percent of infections are asymptomatic and frequently go undetected. The new and highly sensitive molecular diagnostic assays are more reliable than other available tests for detecting chlamydia and can utilize noninvasive specimens such as urine and self-administered vaginal swabs. NIAID-funded researchers have applied these new technologies to screening large populations in Baltimore, in the U.S. military, and in Uganda. The researchers documented extremely high rates of infection ranging from 5 percent to more than 25 percent. With frequent noninvasive urine-based screening, these NIAID-supported scientists have determined a prevalence of 24 percent in high-risk youths and a reinfection rate of more than 15 percent within a 6-month period.

Researchers funded by NIAID plan to continue using population-based studies that incorporate newly developed molecular amplification assays to screen individuals for *C. trachomatis, N. gonorrhoeae,* and other STIs noninvasively. The goal is to better define the epidemiology, prevalence, and incidence of, as well as risk factors for, infection. Cost-effective models will be applied to these data, and NIAID-supported researchers will monitor the effect on the prevention of the sequelae such as PID, ectopic pregnancies, infertility, and trachoma. Additional studies are planned to further examine the immunopathogenesis of chlamydial cervical infections in women with PID and tubal factor infertility using molecular amplification techniques.

Genital Herpes

Genital herpes is an infection caused by the herpes simplex virus, or HSV. There are two types of HSV and both can cause genital herpes. HSV type 1 (HSV-1) most commonly affects the oral area, e.g., the mouth and lips, but it can infect the genital area and cause sores. HSV type 2 (HSV-2) causes the majority of genital

herpes cases. About one in five adults in the United States has genital herpes, but only one-third of those people are aware that they have the virus. The number of Americans with genital herpes infection has increased 30 percent since the 1970s. Moreover, HSV-2 prevalence among 12- to 19-year-old whites is now 5 times higher than it was 20 years ago. In addition, young adults aged 20 to 29 years are now twice as likely to have HSV-2.[3]

Most people who have genital herpes do not know they have it because they never experience any symptoms. However, for these asymptomatic individuals, infection still poses risks. Because the virus can be active but not cause any symptoms to be seen, asymptomatic individuals can transmit HSV to others, although transmission may not be as efficient as when skin sores are visible.

It is believed that a pregnant woman infected with HSV can transmit the virus to her baby. Usually, neonatal transmission of the virus occurs during vaginal delivery, particularly if the woman has become infected with HSV for the first time during the last trimester of pregnancy. Considering that between 20 percent and 60 percent of U.S. women of childbearing age have been infected with HSV-2,[5] the risk of neonatal herpes is significant. To prevent herpes infection of the infant during delivery when visible sores are detected around the mother's cervix, a cesarean section can be performed before the placental membranes break.

Other methods of HSV prevention are currently being investigated, including vaccines, antiviral drugs, and monoclonal antibodies. One such vaccine is an attenuated virus, meaning that the virus has been weakened through mutations so that it is able to provoke an immune response by the body but cannot cause disease. Studies have shown that the vaccine is effective in animal models. The second vaccine consists of an HSV surface protein plus a booster molecule called an adjuvant. This vaccine is being evaluated for prevention of genital herpes in a phase III efficacy trial as a public-private partnership with industry.

NIAID-funded researchers also are exploring animal model systems and technologies that test novel DNA-based vaccines for genital herpes. Initial studies in mice have verified that DNA-based vaccines are highly protective against HSV-2 infection.

With sponsorship by private industry, NIAID researchers conducted a randomized, multicenter, double-blind, placebo-controlled phase III study to evaluate the effect of valaciclovir (brand name Valtrex), an antiviral drug, in preventing herpes transmission. Researchers recruited heterosexual couples discordant for the presence of HSV-2 antibody—that is, one partner had recurrent genital herpes while the other partner did not. A total of 1,500 couples were randomized into the study at approximately 100 outpatient centers in the United States, Canada, and Europe. This clinical study was presented to the Food and Drug Administration (FDA) in support of a new indication for Valtrex to prevent transmission of genital herpes. (At the time of the printing of this report, the FDA has approved the new indication for Valtrex.)

Scientists also are studying HSV 863, a human monoclonal antibody, against herpes simplex virus. *In vitro* and *in vivo* studies showed that HSV 863 is effective both prophylactically and therapeutically against HSV. Subsequent studies are assessing the safety, potency, and pharmacokinetics of HSV 863 in an adult population before the antibody is tested as adjunct therapy for neonatal herpes. Upon completion of these studies, researchers will begin a phase I/II study of HSV 863 in babies with encephalitis and disseminated neonatal HSV infection to further determine the dose to be used in a phase III controlled trial for babies with neonatal HSV infection.

Because about 45 million to 60 million people in this country have genital herpes, this study is important to assess the role of antiviral-suppressive therapy in decreasing herpes transmission. The evaluation of monoclonal antibodies as part of a concomitant therapeutic regimen for babies with neonatal HSV infection also could help battle the persistent problem of neonatal herpes, which is a life-threatening infection despite the availability of antiviral therapies.

In addition to the investigations under way to identify methods to prevent HSV, NIAID researchers are focusing on two major viral processes in their efforts to discover new targets for anti-HSV therapies: viral binding and entry into the host cell and viral DNA

replication. The drugs that currently are used to treat HSV infections act by selectively inhibiting the process of viral DNA replication. NIAID scientists are studying several proteins involved in viral DNA replication to determine whether they might be appropriate targets for more effective inhibitory drugs. In addition, the control of HSV DNA replication in certain cell types, such as neuronal cells, is critical in the process by which HSV becomes latent in these cells. Understanding the mechanisms of latency is key to understanding how to prevent reactivation of the latent virus.

Researchers have learned that HSV attaches to and enters the host cell via a multistep process involving more than 10 viral glycoproteins and several cellular factors. Although many of these factors have been identified, the step-by-step process underlying viral binding and entry into susceptible cells remains unclear. Investigators are working to identify cell molecules that help in binding the virus to cells and to determine how the stable binding triggers subsequent fusion and entry into the cell. These studies are providing important insights into the biology of the virus and are helping to identify new targets for therapeutic interventions.

In addition, research is progressing on the development of natural and synthetic porphyrins and metalloporphyrins. These compounds possess potent and broad-spectrum antibacterial activity. A number of porphyrin compounds have been found to have potent virucidal activity against either HSV-2 alone or both HSV-1 and HSV-2. Moreover, sodium dodecyl sulfate, a detergent found in personal hygiene products used on the skin and oral mucosa, has been found to protect mice from the morbidity and mortality associated with HSV-2 infection.

With regard to neonatal infections, investigators with NIAID's Collaborative Antiviral Study Group significantly advanced the treatment of neonatal herpes virus infections by establishing the safety and effectiveness of a new dose of the standard antiviral drug acyclovir. Despite treatment, children infected with herpes neonatally continue to die and suffer from blindness and other morbidity. To address this continuing mortality and morbidity, researchers conducted a study to determine whether a higher dose of acyclovir could lead to improvement. This study demonstrated that administration of 60 mg/kg/day of acyclovir (double the dose currently approved by FDA) significantly reduced mortality (from 61 percent to 31 percent) in newborns with disseminated HSV, the most severe form of HSV.

Gonorrhea

Gonorrhea is caused by the bacterium *N. gonorrhoeae,* also known as gonococcus. Gonococci infect the same body sites as chlamydia but may be more likely to produce symptoms. Furthermore, when they occur, symptoms tend to be more severe. Among women, the bacteria first infect the cervix; however, as with chlamydia, the bacteria can spread to the uterus and fallopian tubes, causing PID. Symptoms associated with gonorrhea in females include painful urination, increased vaginal discharge, abdominal pain, and abnormal menstrual bleeding. In 2000, the Centers for Disease Control and Prevention (CDC) estimated that more than 650,000 individuals were newly infected with gonorrhea.

An infected pregnant woman may transmit gonorrhea to her infant as the baby passes through the birth canal during delivery. This can result in gonococcal infection of the baby's eyes, throat, or respiratory tract.

A high priority for NIAID is to develop tools to prevent gonorrhea, such as vaccines or topical microbicides (substances that could be used to coat the inside of the vagina where they would kill gonococci and other pathogens). The recent completion of the genomic sequence of *N. gonorrhoeae* will help provide new insights into the pathogenesis of gonorrhea, paving the way for opportunities for new diagnostic, drug, vaccine, and microbicide developments. Microarrays for both *N. gonorrhoeae* and *C. trachomatis* are now available to the research community through NIAID's Pathogen Functional Genomic Resource Center.

Human Papillomavirus

Human papillomavirus is likely the most common sexually transmitted disease among young, sexually active people. At any one time, an estimated 20 million people in the United States have genital HPV infections that can be transmitted to others. Each year, about 5.5

million people acquire a genital HPV infection. Studies show high levels of HPV infection in women, with the highest levels in the younger age groups. The virus sometimes causes genital warts but often infects people without causing symptoms. Thirty distinct types of HPV can infect the genital area. Infection with certain types of HPV has been shown to be the single most important risk factor for cervical cancer.[3]

In collaboration with the Los Alamos National Laboratory, NIAID has established a database of information on the genetic sequences of HPV and related papillomaviruses. In 1998, this effort was expanded and a relational database (STDGEN) was established. This database includes HPV sequences as well as genomes of other pathogens. The database analyzes structure and function relationships within and between pathogens. Acquisition of this genomic information will help pave the way for the development of new diagnostics, therapeutics, and vaccines.

Using the various animal models, NIAID-supported scientists have been testing a new class of antiviral drugs for their effectiveness in treating warts. The most promising candidate so far is cidofovir. On the basis of promising results in animal models, Belgian researchers treated patients with severe recurrent laryngeal papillomatosis.[6] These people had been infected with HPV at birth, and warts continued to grow on their larynx (voice box) into adulthood.

Because of positive results obtained in the Belgian study, NIAID's Collaborative Antiviral Study Group, a network of about 100 clinical sites throughout North America, will begin a clinical trial of cidofovir for treating recurrent laryngeal papillomatosis among children. In addition, two other NIAID-supported groups are conducting studies of cidofovir as a therapy for genital papillomavirus infection. Moreover, another NIAID-funded group is conducting a trial of the antiviral drug ribavirin as a supplement to laser surgery for treating laryngeal papillomatosis.

In a particularly significant development in HPV research, NIAID-supported scientists developed a vaccine that not only protects mice against the development of tumors similar to those that occur with cervical cancer but also cures mice with established tumors. The vaccine causes the immune system to attack an HPV protein that helps transform normal cells into cancer cells. In studies with mice, vaccination protected 80 percent of the mice from the development of tumors and cured mice with small, established tumors.[7]

To develop better therapies for HPV infection, NIAID researchers are investigating the functions of important HPV proteins that control the replication of viral genes and the production of viral proteins and that possibly play a role in the progression of HPV-related tumors.[8] Understanding the role of these proteins in the viral life cycle and in cancer might lead to the design of specific antiviral therapies.

Syphilis

Syphilis is a sexually transmitted infection caused by a bacterium called *Treponema pallidum*. The initial infection causes an ulcer at the site of infection, and the bacterium moves throughout the body, damaging many organs over time. Medical experts describe the course of the disease by dividing it into four stages—primary, secondary, latent, and tertiary (late). An infected person who has not been treated may infect others during the first two stages, which usually last 1 to 2 years. In its late stages, untreated syphilis, although not contagious, can cause serious heart abnormalities, mental disorders, blindness, other neurologic problems, and death.[9]

The bacterium spreads from the initial ulcer of an infected person to the skin or mucous membranes of the genital area, the mouth, or the anus of a sexual partner. It also can pass through broken skin on other parts of the body. The syphilis bacterium is very fragile, and the infection is almost always spread by sexual contact. In addition, a pregnant woman with syphilis can pass the bacterium to her unborn child, who may be born with serious mental and physical problems as a result of this infection. However, the most common way to get syphilis is to have sex with someone who has an active infection.

In 2002, 6,862 cases of primary and secondary syphilis in the United States were reported to CDC. However, syphilis continues to disproportionately affect

African Americans, with reported rates of primary and secondary syphilis more than 8 percent higher for African Americans than for whites.[10]

As part of the Public Health Service's effort to eliminate syphilis in the United States by 2005, NIAID's efforts focus on providing better biomedical tools to prevent and control this disease. These efforts include (1) diagnostic test development, which is intended to create a rapid, inexpensive, easy-to-use test; (2) a clinical research study of oral therapy to treat early-stage syphilis; and (3) development of a syphilis vaccine that would target and prevent systemic infection (including congenital syphilis) and could potentially ameliorate disease progression.

NIAID is currently supporting a clinical research protocol examining a single oral dose of therapy for early syphilis. The goal of the study is to determine whether treating syphilis with azithromycin is as effective as the current recommended treatment, benzathine penicillin G. Azithromycin offers many advantages over benzathine penicillin. Azithromycin is taken orally; benzathine penicillin is administered by often painful injections that can discourage patients from seeking treatment. In addition, the penicillin injections require refrigeration and needles, which can hamper administration in "field" settings. The azithromycin regimen proposed in this study could be administered as direct observed therapy in the field, using strategies modeled after those used to treat tuberculosis.

The long-term goals of all NIAID's syphilis activities are to (1) complement CDC's syphilis elimination program, (2) provide improved biomedical and behavioral tools to achieve and sustain syphilis elimination in the United States, and (3) provide improved tools for prevention and control of syphilis in developing countries. NIAID's research takes into account the limited resources of areas where syphilis is endemic, the social and cultural barriers to accessing effective health care in some of those endemic areas, and the need for sustainable interventions.

Topical Microbicides

A topical microbicide is a preparation (e.g., gel, cream, foam) that is applied to the vagina to kill pathogens, including HIV, being transmitted by either sexual partner. The ideal microbicide would be safe and nonirritating to the mucosal tissues, even if used on multiple occasions in a short period of time. In addition, the microbicide should be inexpensive, unobtrusive, both fast and long acting, easy to store, and appealing to potential users. Topical microbicides should be available in both spermicidal and nonspermicidal formulations so that women would not have to put themselves at risk for acquiring HIV and other STIs to conceive a child.

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 lead to the identification of safe and effective topical microbicides. To that end, the Institute supports six Topical Microbicide Program Projects that focus on the development of these compounds. Also, NIAID recently initiated the Microbicide Preclinical Development Program. This new program, co-sponsored by the National Institute of Child Health and Human Development (NICHD), supports the discovery and preclinical development of novel or under-explored microbicides. To date, NIAID and NICHD each have made three awards. In addition, both Institutes jointly established the Integrated Preclinical/Clinical HIV Topical Microbicide Program to conduct translational research, taking promising concepts into early pilot clinical trials.

NIAID also sponsors Topical Microbicide Workshops to assess the state of current knowledge about preclinical methods and microbicide candidates for preventing the sexual transmission of bacteria, protozoa, and viruses, including HIV. These workshops review the progress of the topical microbicide research, facilitate collaborations among scientists from different disciplines and between academic and private-sector participants, and encourage interactions between FDA regulatory staff and commercial sponsors. The workshops include representatives from the public and private sectors, industry, Government, foundations, and community advocacy groups.

NIAID supports large-scale *in vitro* screening of potential HIV transmission-blocking agents through a contract to the Southern Research Institute facility in

Frederick, Maryland. Potential microbicides are obtained from private-sector, academic, and government sources. The microbicides are tested in several different assays to determine their ability to block HIV transmission from infected T cells to cultures of cells derived from the lining of the human cervix. In the past year, a new assay was developed to monitor the activity of potential microbicides under the conditions that mimic the vaginal environment. To date, more than 1,825 unique compounds have been examined in nearly 4,200 primary and secondary assays to determine their potential as microbicides. The colorless or lightly colored compounds with a high therapeutic index are undergoing additional evaluation to assess their potential for development as topical microbicides. The compounds also are being evaluated to determine whether they cause intravaginal irritation or other adverse effects in experimental animals and to ascertain whether they remain stable in the vagina after delivery.

NIAID has a contract with the University of Washington for microbicide research in nonhuman primates. Researchers evaluated multiple candidate microbicides for safety (effects on surface tissues and microenvironment of the cervix and vagina) in pig-tailed macaques. Several of the candidates also were tested for efficacy against chlamydial challenge in the same pig-tailed macaque model. Some of these microbicides have entered clinical trials in the HIV Prevention Trials Network (HPTN). (See "Transmission of HIV to Women" on page 5.)

A number of promising topical microbicide candidates are in various stages of testing. BufferGel®, an acid-buffering gel, helps maintain the normal acidic environment of the vagina during coitus to disrupt the transmission of acid-sensitive STI pathogens, such as HIV. BufferGel® has been tested in clinical trials through NIAID's HPTN to evaluate its safety and tolerability. The first trial was conducted in the United States, followed by studies in India, Malawi, Thailand, and Zimbabwe. The results of these trials indicate that BufferGel® was nontoxic and well tolerated. Conversely, in a phase III trial in Cameroon that enrolled 1,200 persons, a nonoxynol-9 film was found to have no effect on transmission of HIV, gonorrhea, or chlamydia when provided as part of an overall HIV/STI prevention program. No additional studies of nonoxynol-9 are being conducted because of safety concerns and the potential for increased risk of HIV infection reported in preliminary findings from a phase II Nagel trial during the 13th International Conference on AIDS in Durban, South Africa, in July 2000.

NIAID-supported researchers recently completed a phase I study (HIVNET 020) of PRO 2000, a synthetic compound that works by inhibiting HIV attachment and fusion. Initiated in 1999 in Rhode Island and Pennsylvania and in Durban and Johannesburg, South Africa, the study examined sexually active women at low risk of HIV infection as well as asymptomatic HIV-infected women who were sexually abstinent. The study assessed different strengths of PRO 2000 gel administered intravaginally once or twice a day for 14 consecutive days and found that the product was well tolerated in both groups of women with no serious side effects. All the women indicated their willingness to use the product again if it were shown to protect against HIV infection. Differences in PRO 2000 concentration, frequency of use, and HIV status did not appear to be associated with differences in the prevalence of adverse events. Because PRO 2000 was safe and well tolerated (under the specific conditions of this study), NIAID will continue to evaluate it for widespread effectiveness and potential use.

NIAID also is initiating a phase I study of 9-(2-phosphonylmethoxypropyl)-adenine (PMPA), a microbicide gel that may inhibit HIV replication. PMPA gel has prevented the infection of female monkeys with simian immunodeficiency virus, a relative of HIV, when their vaginas were exposed to the virus.

A particularly novel approach to developing new microbicides involves the use of a bacterial strain called *Lactobacillus crispatus*, which naturally colonizes the vaginas of many women. These bacteria produce chemicals that kill harmful microbes, including those that cause STIs. The colonizing bacteria also are associated with reducing women's risk of getting gonorrhea, HIV infection, and bacterial vaginosis, a type of vaginal inflammation. Other potential compounds that researchers will continue to examine for defense against microbes include chemicals produced by animal cells, such as the protegrins, a family of small proteins

produced by the white blood cells of animals. Researchers supported by NIAID have produced several variants of one protegrin that are able to inactivate gonococci, chlamydia, and HIV without adverse effects on human cells.

NIAID has developed a strategic plan detailing long-range plans for the whole spectrum of microbicide research, from laboratory to clinical trials. This plan was reviewed by a panel of experts this year and is available in printed form and on NIAID's Web site at www.niaid.nih.gov/publications/topical_microbicide_strategic_plan.pdf.

The Role of Sexually Transmitted Infections in Spreading AIDS

Compared with other viruses that cause STIs, such as herpes simplex viruses, human papillomaviruses, and hepatitis B virus, HIV is not easily transmitted. Heterosexual transmission occurs in only 1 of 500 cases of vaginal intercourse in which one partner is infected. However, if either partner has another STI, this substantially increases the risk of HIV transmission. STIs that cause discharge of pus and mucus (e.g., gonorrhea, chlamydial infection) increase the risk from threefold to fivefold, and STIs that cause ulcers (e.g., syphilis, genital herpes) increase the risk up to ninefold.[11]

A number of possible mechanisms may be responsible for these increases. Certainly, the ulcerative STIs disrupt the protective layers of skin and mucosa, which may allow HIV easier access to blood vessels. STIs also increase the number of inflammatory cells in the reproductive system, some of which are targets of HIV.

Whatever the mechanisms, the identification and treatment of existing STIs are clearly one important strategy for reducing HIV transmission. NIAID-supported researchers have demonstrated the effectiveness of this strategy with men infected with both HIV and gonorrhea. As a result of gonorrhea, these men had urethritis (inflammation of the urethra, the canal that carries both semen and urine). The scientists noticed that urethritis greatly increased the HIV load (the amount of virus) in the semen of these men and that treating the gonorrhea and the inflamed urethra reduced the seminal HIV load, even if the patients were not taking drugs for the HIV infection.[12]

HSV-2 is a common viral co-infection in persons with HIV. NIAID-funded studies have suggested that the rate of HIV progression may be affected by HSV reactivation. Thus, daily suppression of HSV may be important for the management of persons with both HSV and HIV. Additional studies are required to determine the effect of HSV suppression on both the rate of HIV transmission and the natural history of HIV.

Glossary

adjuvant—A substance added to an antigen in a vaccine to enhance or modify the immune response to the antigen.

ameliorate—To make better or improve.

antibody—A protein molecule produced and secreted by immune cells in response to an antigen. The antibody binds to the antigen, triggering reactions of the immune system that are designed to eliminate the antigen.

antigen—Any substance that, when introduced into the body, stimulates an immune response.

antiretroviral—A substance that stops or suppresses the activity of a retrovirus such as HIV.

antiviral—Drugs that stimulate cellular defenses against viruses.

assay—The determination of the amount of a particular constituent of a mixture or of the biological or pharmacologic potency of a drug.

atherosclerosis—The progressive narrowing and hardening of the arteries over time.

autoimmune disease—A disease that results when the immune system mistakenly attacks the body's own tissues.

bacterium—A microscopic organism composed of a single cell. Many, but not all, bacteria cause disease.

carcinoma—A malignant growth found in skin or, more commonly, the lining of body organs, for example, breast, prostate, or lung. Carcinomas tend to infiltrate into adjacent tissue and spread (metastasize) to distant organs.

cardiovascular—Pertaining to the heart and blood vessels.

concomitant—Occurring or existing concurrently; accompanying.

culture—The propagation of microorganisms or of living tissue cells in media designed to support their growth.

disseminated HSV—Herpes simplex virus spread over a considerable area; the most severe form of HSV.

ectopic pregnancy—Development of an embryo in a pregnancy location other than the uterus—for example, in a fallopian tube or in the abdominal cavity.

endocrine system—The system of glands and other system structures that controls hormone release.

endometrium—The inner membrane of the uterus.

epidemiology—The science concerned with the factors affecting the frequency and distribution of disease for the purpose of establishing programs to prevent and control their development and spread.

estrogen—A generic term for female sex hormones.

etiologic—Assigning or seeking to assign a cause.

fallopian tubes—A pair of long slender tubes that carry eggs from the ovaries to the uterus.

gene—The functional unit of heredity that occupies a specific place on a chromosome, is capable of reproducing itself exactly at each cell division, and directs the formation of an enzyme or other protein.

hematopoietic—Forming blood or blood cells in the body.

hepatic steatosis—Fatty liver.

histocompatibility—A state or condition in which the absence of immunologic interference permits the grafting of tissue or the transfusion of blood without rejection.

hormone—A chemical formed in one organ or part of the body and carried in the blood to another organ or part. Hormones can alter the functional activity and sometimes the structure of one or several organs.

immune response—The reactions of the immune system to foreign substances.

immune system—A complex system of cells and molecules having the primary function of protecting the body from foreign organisms and substances.

incidence—The rate of occurrence of a disease—for example, the percentage of people who contract a particular disease within a year.

inflammation—Redness, warmth, swelling, pain, and loss of function produced in response to injured tissue. Inflammation results from increased blood flow and an influx of immune cells into the injured area. It initiates the elimination of the injurious agent and the injured tissue.

intrapartum—During labor and delivery or childbirth.

intravaginal—Within the vagina.

major histocompatibility complex molecules—Cell surface molecules that help control the immune response against microbes or tumors. These molecules present antigens to nearby T cells as a flag indicating that a cell is infected or diseased.

metastasize—To spread to another part of the body, usually through the blood vessels, lymph channels, or spinal fluid.

microbicide—Any agent detrimental to, or destructive of, the life of microbes or bacterial organisms.

microorganisms (microbes)—Minute living organisms, including bacteria, viruses, fungi, and protozoa.

molecule—The smallest amount of a specific chemical substance that can exist alone. A molecule consists of one or more atoms—for example, a molecule of water consists of two hydrogen atoms and one oxygen atom.

mucous membrane (mucosa)—A membrane rich in mucous glands. Mucous membranes line body passages and cavities that communicate directly or indirectly with the exterior.

mucus—A slippery secretion produced by mucous membranes that moistens and protects the membranes.

mutation—An alteration of a gene or chromosome that can be inherited.

neonatal—Pertaining to the first 4 weeks after birth.

organism—An individual living being.

pathogen—A microorganism, such as a bacterium, that lives on an animal (or plant) or human as a parasite and produces a disease.

pelvic inflammatory disease—An ascending pelvic infection causing inflammation of female reproductive organs, such as the uterus, fallopian tubes, and ovaries.

perinatal—The time shortly before and after birth.

placebo—An inactive substance that is given to the control group of patients in a clinical trial. The purpose is to compare the effects of medication with that of no medication.

polymorphism—The occurrence of different forms, stages, or types in individual organisms or in organisms of the same species, independent of sexual variations.

prevalence—The percentage of a population that is affected with a particular disease at any given time.

prophylactically—Acting to defend against or prevent something, especially disease; protective.

proteins—Large organic compounds composed of smaller molecules called amino acids.

psychotherapeutic—Related to psychotherapy, or the treatment of mental illness or emotional disturbances.

receptors, cellular—A protein molecule, usually on the cell surface, that binds to a specific factor, such as an antigen.

replication—The process of duplicating or reproducing.

seroincidence—The number of new cases of a given population testing positive on the ELISA test for particular antibodies.

seroprevalence—The rate at which a given population tests positive on the ELISA test for particular antibodies.

syndrome—A group of signs and symptoms that occur together and characterize a particular abnormality.

systemic—Pertaining to or affecting the body as a whole.

systemic lupus erythematosus—An inflammatory disorder characterized by bleeding in the skin and mucous membranes, inflammation of the membrane

enclosing the heart, and possibly involvement of the kidneys and central nervous system. Of unknown cause, but probably an autoimmune disease.

T cells—Small white blood cells that orchestrate or directly participate in immune defenses.

tolerance—A state in which the immune system does not respond to a particular antigen or group of antigens.

tolerogenic—Capable of inducing immunologic tolerance.

topical microbicide—A chemical that can be applied to the surface of the body to kill microorganisms. In connection with sexually transmitted diseases, a topical microbicide would be applied in the vagina or rectum to kill the microbes that cause these diseases.

ulceration—The formation of a local excavation of the surface of an organ or tissue, which is produced by the sloughing of inflammatory dying tissue.

urethra—The canal that carries urine from the bladder to the outside. In men, the urethra also carries semen.

vaccine—A substance that contains antigenic components from an infectious organism. By emulating an immune response (but not disease), a vaccine protects against subsequent infection by that organism.

virus—A submicroscopic microbe that causes infectious disease. Viruses can reproduce only in living cells.

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