The National Institute of Allergy and Infectious Diseases

2007-2008 Biennial Report on Women's Health Research

I. Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) funds basic and applied research to prevent, diagnose, and treat infectious and immune-mediated illnesses that affect the health of women and girls. NIAID involves women in many of its clinical studies on treatment and prevention of autoimmune diseases, human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and sexually transmitted infections (STIs). NIAID also collaborates with other organizations on research initiatives aimed at improving women's health.

This report provides an overview of NIAID's recent accomplishments in women's health research. Investigators engage in basic research, preclinical research, and clinical research in an effort to better understand how women and girls are preferentially susceptible to particular infectious or immune-mediated diseases. Accomplishments include the sponsorship of clinical trials that test possible antiretroviral drugs or topical microbicides to prevent the transmission of HIV to women or their partners; epidemiological studies to explore the cardiovascular health of women infected with HIV; therapeutic studies to examine the effects of antiretroviral drugs, such as protease inhibitors, during pregnancy; basic research on proteins found in the thymus that are known to cause broad autoimmunity against many organs and tissue; as well as preclinical vaccine research for the herpes simplex virus. The breadth of research sponsored by NIAID is aimed at improving and protecting the lives of women and girls in the United States and globally.

The overview of selected NIAID-sponsored women's health activities, as well as scientific advances, is presented here in two separate focus areas: scientific accomplishments and related accomplishments in women's health research. The first section includes accomplishments in research on HIV/AIDS, STIs, and immunology and immune-mediated diseases. Related accomplishments in women's health research include research training, and the women's health research work group. Also included is a section on initiatives, which includes program announcements, requests for application, contracts, and conferences. Sex/gender analysis studies and research on health disparities in special populations are highlighted.

II. Scientific Accomplishments

A. HIV/AIDS

United Nations Joint Programme on HIV/AIDS (UNAIDS)/World Health Organization (WHO) statistics estimate that 33 million people worldwide are infected with HIV. Women face the greatest risk of acquiring HIV due to substantial mucosal exposure to seminal fluids, prevalence of non-consensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners. Most women are infected with HIV through sex with men or injection drug use.

Over the past two years, the number of women and girls infected with HIV has increased in every region of the world, with rates rising particularly rapidly in Eastern Europe, Asia, and Latin America. At the end of 2007, women accounted for 50 percent of all adults living with HIV worldwide, and for 60 percent in sub-Saharan Africa. The U.S. Centers for Disease Control and Prevention (CDC) report that women accounted for over 26 percent of all new AIDS cases reported in the United States in 2005, an increase from 11 percent in 1990.

In addition to the complications of AIDS that affect men, infected women also suffer gender-specific manifestations of HIV disease such as recurrent vaginal yeast infections, pelvic inflammatory disease (PID), genital ulcer disease, severe herpes infections, gender-specific abnormalities related to infection with human papillomavirus (HPV), as well as vulvar and vaginal carcinomas. Drug metabolism also differs in women as compared to men, potentially resulting in differential responses to antiretroviral (ARV) therapy and an increased incidence of drug toxicities in

women. Frequently, women with HIV infections have difficulty accessing health care and carry a large burden of caring for children and other family members who may also be HIV-infected. They often lack social support and face other challenges that may interfere with their ability to adhere to treatment regimens.

NIAID is supporting investigations of the course of HIV/AIDS in women through multiple initiatives including intramural studies; unsolicited research on women and HIV/AIDS; the Women's Interagency HIV Study (WIHS), a long-term cohort study; the Centers for AIDS Research (CFAR) women's health supplement; and clinical trials to investigate gender-specific differences in HIV disease progression, complications, and/or treatment. These clinical trials are being conducted by the Microbicides Trials Network (MTN), the AIDS Clinical Trials Group (ACTG), the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT), the HIV Prevention Trials Network (HPTN), the HIV Vaccine Trials Network, and the International Network for Strategic Initiatives in Global HIV Trials**.**

1. Epidemiological Research

NIAID-supports epidemiological research on:

- The long term natural and treatment history of HIV infection in women; in particular, research that evaluates the impact of ARV therapy on the clinical course of HIV disease
- The effect of hormonal, endocrine, and local factors on HIV viral load and sexual transmission
- Studies of older populations of HIV-infected women to investigate what pathogenic processes are related to HIV, ARV therapy, and/or the aging process
- Characterization of acute clinical events and co-infections and their impact on HIV disease progression
- Studies of the female genital tract compartment including the microenvironment, HIV virology, and immunology of the female genital tract as compared to blood

Scientific Advances

Women's Interagency HIV Study (WIHS) –is the largest observational study of HIV-infected women and includes participants living in six U.S. metropolitan areas. The majority of the more than 3,500 women enrolled in the study are African American and Latina women living in urban areas. The size of the study, the number of recently diagnosed patients, and the availability of stored biospecimens allow the evaluation of clinical outcomes in the era of HAART. Researchers are investigating factors such as the development of AIDS, drug resistance, co-infections, therapy use and treatment effects, metabolic abnormalities and toxicities, hormonal factors, aging, neurocognitive functioning, and physical impairment. This study has yielded major discoveries that have led to a better understanding of how HIV is spread, how the disease progresses, and how it can best be treated. More information is available at: http://statepiaps.jhsph.edu/wihs/.

Risk Factors for Carotid Lesions in Women and Men Taking Highly-Active Anti-Retroviral Therapy (HAART) – WIHS and NIH collaborators explored the risk factors for the development of carotid lesions, a sign of early stage atherosclerosis, in individuals infected by HIV. In 2008, they reported that the immune suppression associated with HIV infection may significantly increase the risk for carotid lesions in women and men. However, the use of HAART was not consistently associated with carotid atherosclerosis, especially in women. Furthermore, the risk for carotid atherosclerosis was not significantly associated with either HIV viral load or a history of clinical AIDS. The findings suggest that maintaining adequate levels of CD4 T-cells, a type of immune cell, may reduce the risk of cardiovascular disease (CVD) among HIV-positive individuals. (AIDS: 22(13): 1615-24, 2008)

Other WIHS Research Findings – WIHS reports in 2008 addressed such topics as the relationship of HAART adherence in women in association with adverse treatment effects (CID: 45: 1377–85, 2007); perception of body fat changes (AIDS Behav: Epub ahead of print, 2008); presence of children in the household (AIDS Patient Care and STDS: In press, 2008; Pediatrics, 121: e787-e793, 2008); and illegal drug use (Am J Drug Alcohol Abuse: 34: 161-170, 2008). Other reports dealt with the relationship between HIV progression and variables such as illegal drug use (AIDS: 22: 1355-1363, 2008) and insulin-like growth factor (J Infect Dis: 197: 319-327, 2008). The importance of illegal drug use in recent WIHS findings (Am J Drug Alcohol Abuse: 34:161-170, 2008; J Acquir Immune Defic Syndr: in press, 2008; AIDS: 22: 1625-1627, 2008; Drug and Alcohol Dependence: 89: 74-81, 2007) reflects the

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fact that about one-third of WIHS participants were infected via shared needles and are also infected with hepatitis C virus.

The Risk of CVD among Women in the WIHS Study Initiating Abacavir – This NIAID-funded study is designed to analyze specimens and associated data from the WIHS biorepository to study risk factors for the development of CVD in women infected with HIV who are taking the ARV, abacavir. Earlier research has shown that women infected with HIV tend to have a higher underlying risk for CVD compared to the general population, partly due to HIV-specific factors. For example, use of ARV drugs may increase the risk for myocardial infarction (MI), possibly in association with inflammation and subclinical atherosclerosis. Investigators will evaluate biomarkers associated with these pathologies in WIHS participants initiating abacavir- and non-abacavir-containing ARV regimens. They will also evaluate the cardiovascular outcomes among women by abacavir treatment history. Investigators also will test samples from the Multicenter AIDS Cohort Study (MACS) biorepository to identify potential gender-specific differences in abacavir response.

2. Prevention Research

a) Seroincidence Study

The Women's HIV SeroIncidence Study (ISIS) (HPTN064) – ISIS is part of the the HIV Prevention Trials Network (HPTN), a worldwide collaborative clinical trials network that develops and tests the safety and efficacy primarily of non-vaccine interventions for the prevention of HIV. ISIS is a multi-site, observational study that will estimate the overall HIV-1 incidence in women at high risk for HIV acquisition in the United States. Investigators will also evaluate laboratory assays for HIV-1; estimate study recruitment and retention rates; describe sexual behaviors, alcohol and drug use, prevalence of domestic violence, and mental health indicators of women at risk for HIV; assess women's preferred recruitment and retention strategies for future studies; describe social, structural and contextual factors to inform future intervention studies; and explore facilitators and barriers to HIV testing among men residing in high-risk areas. In 2009, this HPTN study will begin enrollment of 2,000 women from ten geographically distinct high-risk areas of the United States. Investigators will follow all participants for six to twelve months. More information on this and other HPTN research is available at: http://www.hptn.org/research_studies.asp.

b) Topical Microbicides

There is an intensified need for the development of a safe, effective, and acceptable topically applied chemical and/or biologic barrier to prevent sexually transmitted HIV infection.

NIAID-sponsored research goals support the development of a topical microbicide that:

- Prevents infection and/or viral replication by both cell-free infectious HIV particles and cell-associated infectious particles.
- Is safe and non-inflammatory (causes no irritation to the vaginal/cervical/urethral/rectal epithelium).
- Reduces transmission and acquisition, including potentiation of HIV acquisition by other STIs.

Scientific Advances

Use of Tenofovir for Simian Immunodeficiency Virus Prevention in a Non-Human Primate Model – Research in a non-human primate model suggests that the vaginally formulated microbicide tenofovir (TFV) gel may help prevent rectal transmission of HIV. The investigators evaluated the efficacy of the gel applied rectally prior to rectal exposure with simian immunodeficiency virus (SIV) in rhesus macaques. Eight of nine macaques in the study were protected from infection. This nonhuman primate study provides the first evidence that an ARV-based, vaginally formulated topical microbicide may protect against rectal transmission of HIV. The data also suggest that TFV drug levels in the blood may serve as surrogate markers in clinical trials of microbicide efficacy. Furthermore, the finding suggests the possibility of a novel pathway for using microbicides to induce a protective immune response similar to that of a vaccine. (PLoS Med: 5(8): e157, 2008)

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Clinical Trials

Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women (HPTN 035) **–** The study will evaluate the safety and efficacy of BufferGel and 0.5% PRO2000/5 Gel (P) when applied vaginally by women at risk for sexually transmitted HIV infection. Enrollment is complete to this international HPTN study with sites in the United States, Malawi, Zimbabwe, Zambia, and South Africa. Follow-up will continue until all participants have used one of the microbicides for at least 12 months. Data analysis is ongoing and results are expected in 2009. More information on this and other HPTN research is available at: http://www.hptn.org/research_studies.asp.

Phase II Expanded Safety and Acceptability Study of the Vaginal Microbicide 1% Tenofovir Gel (HPTN 059) **–** This study will assess the safety of TFV gel for vaginal use in HIV-uninfected women when used once daily or prior to intercourse. Enrollment in this HPTN clinical trial set in New York, New York; Birmingham, Alabama; and Pune, India is complete and follow-up is ongoing

Phase I Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel™) Applied Vaginally in Sexually Active Young Women" (MTN-004) **–** The MTN uses a focused microbicide research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission. This MTN clinical trial is ongoing at two study sites, one in Tampa, Florida, and one in San Juan, Puerto Rico. Both sites are part of the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD)-funded Adolescent Trials Network. This study will evaluate the safety of Vivagel applied twice daily for two weeks in sexually active 18-24 year old women. Study investigators plan to enroll a total of 40 women. More information on this and other MTN research is available at http://www.mtnstopshiv.org/node/studies.

Phase II Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir (MTN-001) **–** This MTN clinical trial will enroll 144 women at seven clinical sites in the United States and Africa to examine adherence and acceptability of six weeks each of oral, vaginal, and dual use of tenofovir. The trial will include pharmacokinetic studies.

Phase IIB Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate (DF) Tablet and Tenofovir DF-Emtricitabine Tablet for the Prevention of HIV Infection in Women (MTN-003) **–** The MTN is planning this clinical trial, also known as the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial. Beginning in early 2009, investigators expect to begin enrollment of 4,200 women in Africa to test a pre-exposure prophylaxis (PrEP) approach to HIV prevention, especially in heterosexual sub-Saharan African women. VOICE is the only PrEP study to focus exclusively on women. This large randomized clinical trial will compare the safety and effectiveness of two approaches to HIV prevention: (1) use of an oral ARV pill (either TFV or Truvada®) once a day, and (2) use of ARV-based vaginal microbicide TFV gel on a daily basis. VOICE will also evaluate the potential for and prevalence of drug resistance in women who acquire HIV while participating in the study. Two sub-studies will examine bone mineral density (VOICE B) and the impact of individual and community factors on trial retention and on treatment adherence (VOICE C). This is the first study to evaluate the effectiveness and acceptability of oral and vaginal forms of PrEP in the same study.

The Sexually Transmitted Infections Clinical Trials Group (STI CTG) – The STI CTG has completed enrollment to a Phase I trial to evaluate the safety of a twice daily, vaginally applied microbicide gel (SPL 7013). This topical microbicide is designed to prevent sexually transmitted infections including genital herpes and HIV. More information on this and other STI CTG trials is available at: http://www.stictg.org/protocols.html.

Integrated Preclinical/Clinical Program-HIV Topical Microbicides Awards – Several studies funded through this award program were developed, initiated, and/or completed in 2008. They include an ongoing trial of rectal health, behaviors and microbicide acceptability; a safety and acceptability study of UC-781, a vaginal microbicide gel for rectal application in individuals not infected with HIV-1; a study of the pharmacokinetics and pharmacodistribution of oral TFV and vaginally formulated TFV gel used rectally; and a comparative study of the

mucosal toxicity, colorectal distribution, and participant acceptability of three different preparatory enemas. More information is available at:
http://www3.niaid.nih.gov/topics/HIVAIDS/Research/prevention/research/Microbicides/funding.htm.

Investigator-Initiated Prevention Clinical Trials – NIAID also funds HIV prevention trials through investigator-initiated awards. Various studies are investigating the safety and persistence of 0.1% UC-781 vaginal gel in HIV-1 negative women; the effect of repeated applications of TFV gel on mucosal mediators of immunity; use of optical coherence tomography as a safety imaging system for microbicide use; intrinsic antimicrobial activity of cervicovaginal secretions in women at low risk for HIV-1 infection; and post-coital anti-viral activity of cervicovaginal secretions following vaginal application of the microbicide 0.5% PRO 2000/5 Gel (P).

c) Vaccine Research

Vaccines contain killed or modified microorganisms or parts of microorganisms that can stimulate an immune response in the body to prevent future infection with the same or similar microorganisms. Despite extraordinary advances in understanding both HIV and the human immune system, an effective vaccine HIV vaccine continues to elude researchers. NIAID conducts and supports basic research in areas such as infectious diseases, microbiology, and immunology to generate the knowledge essential for developing safe and effective vaccines for the prevention of HIV infection.

Clinical Trials

Longitudinal Studies of Women at High Risk for HIV-1 Infection to Inform HIV Vaccine Trial Participation (HVTN 906; HVTN 907) **–** The NIAID-funded HVTN is planning two studies on the feasibility of recruiting and retaining women at high risk for HIV infection for participation in vaccine trials. HVTN 906 will enroll women who reside in areas of high HIV prevalence or who engage in high-risk behavior in New York, New York; Philadelphia, Pennsylvania; and Chicago, Illinois. Investigators will also enroll women who are partners of men from subgroups with a high prevalence of HIV. HVTN 907 will enroll women living in the Caribbean (Haiti, Dominican Republic, and Puerto Rico) and will focus on female commercial sex workers with demographic, behavioral, or other social factors associated with high prevalence of HIV. Investigators will also assess HIV prevalence in both studies. More information on HVTN research is available at: http://www.hvtn.org/index.html.

d) Prevention of HIV in Individuals Infected with Herpes Simplex Virus Type 2 (HSV-2)

Scientific Advances

Tests of Acyclovir for HIV Prevention in Women and Men Infected with HSV-2 – Research suggests that HSV-2 infections are associated with an increased risk for HIV infection. This HPTN study investigated whether suppression of HSV-2 with the antiviral drug acyclovir would reduce the risk of HIV-1 acquisition in HSV-2-positive women and men who have sex with men. The researchers reported that suppressive therapy with standard doses of acyclovir did not reduce HIV acquisition in this population. This study and other research emphasize the need for novel strategies to interrupt interactions between HSV-2 and HIV-1. (Lancet: 371: 2109-19, 2008)

Clinical Trials

Ancillary Study: Prospective Cohort Study of HPTN 039 Seroconverters: The Effect of HSV-2 Suppression on HIV-1 Viral Set Point (HPTN 309-01) **–** HPTN researchers are investigating factors affecting medication adherence and its measurement using data from a completed HPTN trial of acyclovir for HIV prevention in individuals infected with HSV-2. Results are expected in early 2009.

Effectiveness of Acyclovir in Suppressing HIV Viral Load in Women Coinfected With HIV and HSV-2 – Scientists are analyzing data from this NIAID-supported study conducted by the Comprehensive International Program for Research on AIDS (CIPRA) Peru Project. This study examined the use of acyclovir for the suppression of HIV viral load, and mucosal shedding in women co-infected with HIV and HSV. The results of this analysis are expected in early 2009. More information is available at: http://clinicaltrials.gov/show/NCT00371592.

e) Prevention of Mother-to-Child Transmission (PMTCT) of HIV

According to WHO, the vast majority of all HIV-infected infants and children acquire the virus from their mothers before or during birth or through breastfeeding. Most mother-to-child-transmission (MTCT) occurs late in pregnancy or during birth. Currently, the United Nations Children's Fund (UNICEF)/WHO recommend that infants born to HIV-infected mothers who do not have access to acceptable, feasible, affordable, sustainable, and safe (AFASS) replacement feeding should be exclusively breastfed for at least six months. NIAID is conducting studies on the safety and pharmacology of potent drug combinations for PMTCT in HIV-infected pregnant women. NIAID-sponsored research goals on PMTCT focus on:

- Defining the mechanisms and risk factors for HIV transmission to children and adolescents and from mother to infant as well as risks for disease progression within the framework of clinical studies and trials.
- Developing and testing additional ARV strategies to prevent mother-to-infant HIV infection through clinical trials in the United States and international settings.
- Developing interventions for prevention of HIV transmission via breast milk in settings where breastfeeding is the best assurance for infant nutrition.

Scientific Advances

Use of Nevirapine to Decrease HIV Transmission through Breastfeeding – Three coordinated studies in Ethiopia, India, and Uganda assessed whether giving daily nevirapine (NVP) to breastfed infants through six weeks of age can decrease HIV transmission. Overall, these studies showed that this treatment regimen significantly reduced risk of HIV transmission at six weeks of age; the reduction at six months of age was not statistically significant. The data suggest the need for a longer course of daily NVP to prevent HIV transmission via breast milk through six months of age in settings where AFASS criteria are not met. These findings provide key guidance for designing extended treatment trials. (Lancet: 372 (9635): 300-13, 2008)

Clinical Trials

The Effects of Single Dose Nevirapine (SD NVP) on Future Treatment Options for Women and Children – The ACTG and IMPAACT are cooperating with the HPTN and Department of Defense (DoD) to conduct clinical trials on this topic. "Optimal Combined Therapy after Nevirapine (NVP) Exposure" (ACTG 5208), a randomized clinical trial set mainly in Africa, is evaluating the effects of exposure to SD NVP on HAART treatment outcomes. A parallel study (PACTG 1060) will investigate the effects of SD NVP on ARV therapy treatment outcomes in infants. A study (ACTG 5207) conducted in Africa, India, and Haiti and one in Thailand (PACTG 1032) will explore strategies to minimize viral resistance to ARV therapy and assess the impacts of viral resistance after SD NVP. Another study (ACTG 5227) will examine whether the impact of HAART in women for treatment of HIV is affected by prior exposure to HAART for PMTCT. More information on ACTG research is available at http://www.aactg.org/

3. Therapeutics Research

Scientific Advances

The Safety of Depot Medroxyprogesterone in HIV-Positive Women on ARV therapy – ACTG investigators reported findings from a clinical trial examining the safety of the contraceptive depot medroxyprogesterone (DMPA) when used with ARV therapy regimens. They showed that DMPA-related adverse events in ARV-treated women who are infected with HIV-1 were similar to adverse events reported in women not infected with HIV. There were no differences in adverse events observed among the women in the different treatment regimens, indicating that concomitant use of ARV therapy and DMPA in this population is safe. (Contraception: 77 (2):84-90, 2008; Epub 2007 Dec 21)

The Effects of Protease Inhibitors in Pregnancy – An ACTG study recently showed that use of protease inhibitors (PIs), a type of ARV, do not increase risk of glucose intolerance or insulin resistance among pregnant women infected with HIV. This multicenter, prospective, observational study found that body mass index, Hispanic

ethnicity, and maternal age, but not PIs, were associated with glucose intolerance. Use of PIs was not associated with any differences in insulin resistance or pancreatic beta-cell function. (Am J Obstet Gynecol: 196 (4): 331.e1-7, 2007)

The same study showed that pregnancy outcomes were not different between women taking HAART regimens containing PIs compared with non-PI-containing HAART regimens. The data did show increases in total cholesterol and triglycerides in the women receiving PI-containing HAART, and higher triglyceride levels were associated with lower birth weights of infants. Overall, these data support the continued use of PIs during pregnancy. Further study is needed on the clinical importance of the lipid changes and their impact on birth outcomes. (Obstet Gynecol: 110 (2 Pt 1): 391-7, 2007)

Clinical Trials

Clinical Trials of ARV Therapy during Pregnancy – Ongoing and planned ACTG and IMPAACT treatment trials include a study of the pharmacokinetics of the ARV Efavirenz in the last trimester of pregnancy; a study of the pharmacokinetics of contraceptives used in conjunction with newer ARV drugs; an evaluation of gender differences in HAART responses evaluated in large naïve treatment trials (ACTG 5095, ACTG 5142, and ACTG 5202); and an investigation of the toxicities and complications of the use of an HPV vaccine in HIV-infected girls (P1047) and women (ACTG 5240).

Osteoporosis in HIV-Infected Postmenopausal Women (R01 AI 065200) **–** This ongoing investigator-initiated clinical trial is examining the impact of traditional risk factors for osteoporosis as well as characteristics of HIV infection and ARV therapy on the prevalence of osteoporosis and the rate of bone loss in HIV-infected postmenopausal African American and Hispanic women.

Sex and Disease-Dependant Nucleoside Analog Toxicity (R01 AI 064029) **–** This investigator-initiated clinical trial will compare concentrations of nucleosides in the cells of men and women on nucleoside analog-containing ARV therapy regimens. This study seeks to explain gender differences in adverse events such as localized loss of fat tissue and fat accumulation. Investigators will also evaluate gender differences in the effects of nucleoside analogs on the mitochondria, which are cellular organelles involved in energy production.

4. The Centers for AIDS Research (CFAR)

CFAR is a unique program that provides infrastructure to support a multidisciplinary peer-reviewed HIV/AIDS research in an environment that coordinates studies, promotes communication, provides shared services/expertise, and funds short-term feasibility studies that cannot be funded easily by other mechanisms.

Several pilot projects were funded through the **CFAR Developmental Core**. The “Pilot Study of HIV in Women Attending a Women's Health Clinic in Mumbai, India” will gather data on HIV prevalence, risk behavior, and knowledge, attitudes, and beliefs about HIV-infection. “HIV Prevention in Xhosa Women” will test an HIV intervention tool adapted for Xhosa-speaking women in South Africa. "HIV Prevention for Women: Barriers, Facilitators, and the Media's Role" will examine sociocultural factors of the HIV epidemic in African American women in Boston, Massachusetts. Other projects include "Genotypic Resistance after Pregnancy-Limited Combination Antiretroviral Therapy” and "Exploring the Immunologic and Virologic Differences between Pre and Post Menopausal HIV-positive Women." More information on CFAR research is available at: http://www3.niaid.nih.gov/research/cfar/.

B. Sexually Transmitted Infections

The prevention and treatment of sexually transmitted infections (STIs) are critical global and national health priorities because of their disproportionate and devastating impact on women and infants and their inter-relationships with HIV/AIDS. The CDC reported in 2006 that about 19 million new STIs occur in the United States each year at a cost of nearly $15 billion. The CDC report, Sexually Transmitted Disease Surveillance 2007, shows persistent racial disparities in the cases of chlamydia and gonorrhea and a particular burden of diseases among women in the United States.

NIAID supports a broad array of biomedical research for more effective prevention and treatment approaches to control STIs. This includes:

- Research for safe and effective vaccines, topical microbicides, therapeutics, and strategies for preventing and treating STIs and resulting conditions;
- Basic research on pathogenesis, immunity, molecular and structural biology of sexually transmitted pathogens and the impact of STIs in various populations; and
- Development of better and more rapid diagnostics.

1. HPV

HPV is a group of viruses that includes more than 100 different strains. HPV is of clinical and public health importance because persistent infection with certain oncogenic types can lead to cervical cancer, which is one of the most common cancers in women worldwide. In 2006, the Food and Drug Administration (FDA) licensed an HPV vaccine, Gardasil®, for use in females, ages 9-26 years. Gardasil® is the first vaccine developed to prevent cervical cancer, precancerous genital lesions, and genital warts due to HPV types 6, 11, 16 and 18. The CDC recently reported that approximately 25 percent of adolescent females aged 13 to 17 years old initiated the vaccine series in 2007. (MMWR, 57: 1100-1103)

2. Trichomoniasis

Trichomoniasis is one of the most common STIs. An estimated 7.4 million new cases of trichomoniasis occur each year in men and women in the United States. Trichomoniasis infection commonly occurs in a woman's vagina, resulting in a vaginal discharge, vaginal odor, discomfort during sexual intercourse, and urination, irritation and itching of the genital area and, in rare cases, lower abdominal pain. Both men and women with trichomoniasis have an increased susceptibility to HIV infection and many transmit HIV to their sexual partners. Pregnant women with the infection may deliver a low weight or premature infant. Although prescription drugs cure trichomoniasis, drug resistance has become an increasing concern.

Scientific Advances

Scientists Sequence Genome of Parasite Responsible for Trichomoniasis – NIAID-sponsored researchers have decoded the genetic makeup of the parasite that causes trichomoniasis, revealing potential clues as to why the parasite has become increasingly drug-resistant and suggesting possible pathways for new treatments, diagnostics, and a potential vaccine strategy. (Science 315: 207-212, 2007)_

3. Genital Herpes

There are two types of herpes simplex virus (HSV) and both can cause genital herpes. HSV type 1 (HSV-1) most commonly infects the lips, causing sores known as fever blisters or cold sores, but it also can infect the genital area and produce sores. HSV type 2 (HSV-2) is the usual cause of genital herpes, but it can also infect the mouth. HSV-2 is more common in women than in men. Genital HSV infections can present serious health consequences including lifelong recurrent episodes of painful, genital lesions; increased likelihood of HIV transmission and acquisition; and for women, possible transmission to fetus or neonate that can result in neonatal brain damage or death.

Scientific Advances

Preclinical Research on Genital HSV-2 Vaccines – NIAID has supported testing of several vaccines for the prevention or reduction of genital HSV-2, including a vaccine containing a single protein from HSV-2 (HSV-2 glycoprotein D). Two randomized, controlled clinical trials of this vaccine demonstrated a lower rate of HSV-2 infection in women who were not previously infected with HSV-1. However, the vaccine was not effective in men or in women who were previously infected with HSV-1. NIAID scientists also are evaluating two recently developed candidate HSV-2 vaccines that performed well in preclinical testing. The demonstrated safety of one of

these vaccines in highly immunocompromised animals makes it an excellent candidate for studies in humans. (Vaccine: 26: 4034-40, 2008)

Clinical Trials

Herpevac Clinical Trial for Women – This pivotal Phase III clinical efficacy trial of a vaccine for the prevention of genital herpes has enrolled over 8,300 women at approximately 50 sites in the United States and Canada. This study is a public-private partnership with GlaxoSmithKline. More information is available at http://www.niaid.nih.gov/dmid/stds/herpevac.

4. Chlamydia

Chlamydia trachomatis infections are among the most prevalent of all STIs. In women, chlamydial infections may result in PID, which is a major cause of infertility, ectopic pregnancy, and chronic pelvic pain. The rate of reported chlamydial infection is greater among women than men, and adolescent women are at the highest risk of infection.

Scientific Advances

Discovery of DNA Transfer in *Chlamydia trachomatis* – Basic research studies on *C. trachomatis* are hampered by the fact that it grows exclusively in mammalian cells and has proven resistant to transformation, a cornerstone molecular biology research technique in which foreign DNA is inserted into bacteria to cause the bacteria to produce the proteins encoded by the foreign genes. NIAID-supported researchers are conducting laboratory studies to determine whether transformation will be possible in *C. trachomatis*. Their research may lead to discovery of a way to accomplish successful transformation in *C. trachomatis* and thus advance this important area of research. (J Bacteriol: 189: 991-1003, 2007)

Towards the Goal of an Attenuated Chlamydia Vaccine – Reproductive tract complications of *C. trachomatis* infection are caused by an aggressive immune response that damages the reproductive tract, but leaves the bacteria unharmed. Scientists have long known that a related bacterium, *C. muridarum*, causes a similar disease in mice, including reproductive tract pathology. NIAID-supported researchers recently noticed that most strains of both *C. trachomatis* and *C. muridarum* contain an extra piece of DNA known as a plasmid. Furthermore, they discovered that removal of the plasmid DNA from the *C. muridarum* bacteria made the bacteria less virulent and the plasmid-free strain did not cause reproductive tract pathology in the mice. In addition, infection with the plasmid-free strain protected mice from subsequent infection with the virulent, plasmid-containing strain. Further research will determine whether a plasmid-free strain of *C. trachomatis* could be used to create an attenuated chlamydia vaccine for humans. (J Immunol: 179: 4027-4034, 2007)

Cost Effectiveness of Chlamydia Screening in STI Clinics – NIAID collaborated with University of Massachusetts Medical School and The Johns Hopkins University to compare the cost-effectiveness of chlamydia screening strategies in an STI clinic setting. They reported that self-collected vaginal swabs tested by nucleic acid amplification tests (NAATs) was the least expensive and most cost-effective screening method. Nearly half of the women in the study preferred self-vaginal sampling, almost 30 percent preferred physician-collected cervical sample, and 25 percent preferred self-collected urine sampling. The study also showed that limiting speculum exams to women who require a Pap smear or who present with symptoms, especially abdominal pain, results in substantial health care savings while detecting 97.2 percent of infections. Researchers concluded that providing women with non-invasive screening not only respects the desires of many patients to avoid a speculum exam, but is also cost-effective. (Sexually Transmitted Diseases: 35: 649-655, 2008)

C. Immunology and Immune-Mediated Diseases

NIAID supports investigation of immunology and immune–mediated diseases and their effect on women's health. The goal of this research is to increase the health and well-being of women by developing new methods to prevent and treat autoimmune diseases, enhance graft survival in women, and prevent the immunologic causes of infertility.

1. Autoimmune Diseases

a) Multiple Sclerosis

About 250,000 to 350,000 Americans have multiple sclerosis (MS), and women are affected almost twice as often as men. MS is characterized by scarring of the myelin in the brain and spinal cord, causing varying degrees of neurological impairment depending on the location and extent of the scarring. Although the cause of MS is unknown, scientific evidence increasingly suggests that genetics may play a role in determining a person's susceptibility to MS. There are several treatments to alleviate the symptoms of MS but no cure.

Scientific Advances

Risk Alleles for MS Identified by a Genome-wide Study – Scientists who analyzed the genomes of patients with MS and their family members identified several genes associated with inherited risk for developing MS. Some of these genes help the body to distinguish between self and non-self and others help to control inflammation. These results enhance the understanding of the causes of MS and may suggest avenues for treatment of MS and other autoimmune diseases. (*NEJM* 357:851-862. 2007)

Proteomic Analysis of Active MS Lesions Reveals Therapeutic Targets – Current treatments for MS involve broad suppression of the autoimmune response. The development of more targeted treatments will require a better understanding of the mechanisms of the disease. In this study, investigators examined MS lesions in brain tissue taken at autopsy and identified a set of proteins unique to individuals with chronic active MS lesions, including five proteins known to play a role in blood coagulation. The researchers also discovered that substances that inhibit the activity of these five proteins lessened symptoms in a mouse model of MS. This research provides potential biomarkers for MS diagnosis and suggests that personalized, targeted interventions in early stage disease may help prevent further damage to the nervous system. (Nature: 451: 1076-81, 2008)

Copaxone® for Modulation of Central Nervous System Autoimmune Disease – NIAID-supported scientists used an MS mouse model to explore how the FDA-approved drug Glatiramer acetate (Copaxone®) reduces the symptoms of MS. They showed that Copaxone® promoted the development of a specific type of anti-inflammatory immune cell called type II monocytes. These cells, in turn, modified their output of inflammatory molecules, which led to the generation of T regulatory cells, a type of immune cell that can ameliorate MS-like symptoms and central nervous system inflammation. This improved understanding of how Copaxaone® works may lead to the development of new and more effective forms of this drug. (Nat Med: 13: 935-43, 2007)

Role of the Aryl Hydrocarbon Receptor in Autoimmune Disease – Research has shown that a relative imbalance in two types of immune cells, T regulatory cells (Tregs) and another type of T cell called TH17 cells, may be involved in autoimmune disease. TH17 cells cause inflammation, while Treg cells have the opposite effect of dampening the immune response. Therefore, when TH17 cells are overly active and/or Treg cells are underactive, autoimmune symptoms may develop. NIAID-supported researchers recently showed in a mouse model of MS that a protein called aryl hydrocarbon receptor (AHR), which is present in both types of T cells, can interact with two different molecules that cause opposing effects, and helps control the balance between Treg and TH17. This research has identified the AHR protein as a possible target for therapeutic drugs for MS. (Nature: 453: 65-71, 2008)

b) Lupus

Systemic Lupus Erythematosus (SLE), more commonly known as lupus, is a chronic inflammatory autoimmune disease. Inflammation caused by lupus can affect many body systems, including the joints, skin, kidneys, blood cells, heart, and lungs. Lupus affects approximately 239,000 Americans and occurs more frequently in women than men. African-American women are affected more often than Caucasian women.

Scientific Advances

The Role of B Cell Maturation in SLE – NIAID-supported investigators identified a new “checkpoint” in the maturation of B cells, which are a type of immune cell. They studied a mouse model in which the lack of two proteins, located on the surface of the B cell, leads to the development of lupus. They showed that the absence of these proteins, called Cbl and Cbl-b, led to a faster rate of B-cell maturation and made the B cells less tolerant of self proteins. These findings provide a new target for designing therapeutic intervention against autoimmune diseases

such as SLE. (Immunity: 26: 567-78, 2007)

c) Systemic Sclerosis

Systemic sclerosis (or scleroderma) is group of autoimmune diseases in which the immune system is thought to stimulate cells called fibroblasts, which then produce too much collagen. Systemic scleroderma is the form of the disease that not only includes the skin, but also involves the tissues beneath, the blood vessels, and the major organs. The excess collagen forms thick connective tissue that can interfere with the function of affected organs. An estimated 40,000 to 165,000 people in the United States have this disease, and women are affected more than men, especially middle-aged women and African-American women.

Clinical Trials

High-dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Severe Systemic Sclerosis: Long Term Follow-Up of the U.S. Multicenter Pilot Study – This study is assessing the safety and potential usefulness of a therapy for systemic sclerosis that destroys the malfunctioning immune system and replaces it with immature immune cells, which develop into a healthy immune system. Preliminary results show improved overall function and general stability of organ function over a period of approximately four years. (Blood 110:1388-96, 2007)

d) Understanding the Causes of Autoimmune Diseases

NIAID supports research to elucidate the causes of autoimmune diseases. This research is critical to inform the development of interventions to prevent, diagnose, and treat these illnesses.

Scientific Advances

Role of Extra-Thymic AIRE-Expressing Cells in Autoimmune Disease – Researchers recently discovered that a protein known as AIRE, which was thought to be located only in the thymus, also occurs in other parts of the body in mice. In the thymus, AIRE plays a key role in the removal of immune T cells that can recognize self proteins. Mutations in thymus AIRE protein are known to cause broad autoimmunity against many organs and tissues. In this research, investigators found AIRE protein in cells in the spleen, lymph nodes, and Peyer's patches (lymph nodes found in the gut) that recognize additional proteins from the self. Their findings suggest that these cells may also be involved in the development of autoimmunity and may provide new therapeutic approaches for autoimmune diseases. (Science: 321: 843-7, 2008)

2. Preventing Immune-Mediated Pregnancy Complications

Even though a fetus expresses both maternal (self) and paternal (non-self) genes, the fetus normally does not elicit an immune response from the mother, allowing it to develop through gestation until birth. Failure to develop this immune tolerance is a possible cause for recurrent miscarriages, high mortality and morbidity rates at birth, as well as long term developmental delay and metabolic disorders during adult life.

Scientific Advances

Maternal Immune Response to Fetal Tissue – Researchers used a mouse model to explore the mechanisms used by the maternal immune system to recognize fetal tissue. They found that cells of the fetus did not make a set of proteins, called major histocompatibility class I proteins. Because these proteins were absent, the maternal immune cells did not recognize the fetus as foreign, and therefore did not mount an immune attack against the fetus. These findings improve the understanding of the immunology of pregnancy and early pregnancy failure, and potentially of transplantation and autoimmune disease. (Journal of Clinical Investigation: 117 (5): 1399-1411, 2007)

III. Related Accomplishments in Women's Health Research

A. Research Training and Career Development

Primary Caregiver Technical Assistance Supplements (PCTAS) – To support the career development of young investigators, NIAID sponsors the PCTAS program to provide technical support to postdoctoral scientists who have primary caregiver responsibilities to children or aging parents. Principal investigators with NIAID research grants are eligible to apply for technical support for a postdoctoral scientist for a period of one to two years. The program has been well received by the research community, and three awards were made in the past two years.

Strengthening International AIDS Research on Women and Children – Through an NIAID-sponsored grant on HIV Research in Women and Children, the University of Washington CFAR has provided funds to eight international sites conducting innovative HIV research on women and children in Kenya, Mozambique, and Peru. Studies include investigation of MTCT and HAART research, microbicide and prevention research, and vaginal infection research.

Mentoring International Investigators on HIV Research and Women's Health – The NIAID-sponsored HIV and Women's Core grant at the Tufts University and Brown University CFAR provides mentoring to international investigators conducting research related to HIV and women. The Core also helps mentor Brown University students, residents, and fellows interested in international work related to HIV and women in South Africa, Kenya, Cambodia, the Philippines, and Cape Verde.

B. Trans-NIAID Women's Health Research Workgroup

The Trans-NIAID Women's Health Research Workgroup focuses on women's health and gender-based research activities that advance the mission and research priorities of NIAID, identifies gaps in research, and provides recommendations for future women's health research opportunities. The Workgroup:

- Advises NIAID on the coordination of women and gender-based research across the Institute
- Develops a common framework for identifying and assessing women and gender-based research
- Encourages trans-NIAID and trans-NIH collaborations on women and gender-based research activities
- Coordinates a seminar series highlighting issues and advances in women's health research

IV. Initiatives

A. Initiatives in HIV Pathogenesis Research

1. Program Announcements

Transmission and Pathogenesis of HIV in Women – NIAID released this program announcement (PA) in June 2008 to enhance the knowledge of transmission and pathogenesis of HIV infection in women through the study of biologic mechanisms that impact HIV transmission, acquisition, progression, and manifestations in women. The first round of awards is expected to be made in early 2009. (PAR-08-170)

B. Initiatives in Topical Microbicide Research

1. Request for Applications

Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM) – This request for applications (RFA), sponsored by NIAID and the National Institute of Mental Health (NIMH), was issued in 2007 and 2008 to stimulate iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The revised RFA is harmonized with the Microbicide Innovation Program (MIP). New awards will examine activity and pharmacodynamics of long-acting acceptable microbicides; support basic and comparative studies of inhibition of the HIV-related protein CCR5 to prevent HIV transmission; and pursue development of a practical microbicide based on HIV entry inhibitors. (RFA-AI-08-057)

Microbicide Innovation Program (MIP) – NIAID supports MIP in coordination with the Office of AIDS Research (OAR) and the NIH ORWH. MIP supports research to advance the development of new microbicide approaches

through preclinical and basic research; discovery and exploration of microbicides (singly or in combination) to prevent HIV or STIs that increase risk for HIV acquisition; emerging technologies or models to improve assessment of microbicide safety, efficacy, and acceptability; and exploration of complex prevention strategies that use microbicides in combination with other prevention strategies.

2. Requests for Proposals

Partnerships for Topical Microbicides Program – The five awards supported by this request for proposals (RFP) serve to link industry and academic or other non-profit organizations to advance promising topical microbicide candidates from the conceptual stage through development for testing in clinical trials. The focus of these partnership agreements is to develop a potential microbicide with a proposed dual indication, i.e., prevention of HIV and an STI, or prevention of two STIs. (RFP-AI-04-047)

C. Initiatives in STI Research

1. Request for Applications

Partnerships for Point-of-Care (POC) Diagnostic Technologies for Nontraditional Health Care Settings (U01) – In FY 2008, NIAID released an RFA calling for applications targeting product development activities that will lead to new or improved POC diagnostic technologies for infectious disease-causing pathogens or toxins in nontraditional healthcare settings. The definition of nontraditional health care settings includes the home, rural and urban community public health care clinics, and temporary health care clinics established in response to a natural or man-made disaster. NIAID expects to make awards in FY 2009. (RFA-AI-08-003)

2. Research Enhancement Awards Program (REAP)

Biochemical Analysis of Papillomavirus Replication – This investigation of papillomavirus genome replication received an ORWH REAP award in 2007 and is now funded by NIAID. The investigators are using genetic, biochemical, and structural analyses of the viral proteins and DNA segments called sequence elements that are required for viral DNA replication. Papillomaviruses are very important causative agents of human disease, including cervical cancer. A deeper understanding of the life cycle in general, and DNA replication in particular, is critical to the understanding of this disease, its transmission, and ultimately for the development of effective therapeutic measures. The viral DNA replication machinery to be elucidated in this research presents one of the few potential targets for drug therapy. (1 R01 AI072345-01A2)

D. Initiatives in Autoimmune Disease

1. Program Announcements

Advancing Novel Science in Women's Health Research – NIAID is a cosponsor of this ORWH-led initiative. In 2008, this initiative funded a team of scientists to investigate whether estrogen receptors in key immune regulatory cells may mediate sex bias in lupus. Specifically, the investigators will develop a novel mouse model to explore how estrogens and their receptors regulate the function of two types of immune cells, B cells and dendritic cells, in lupus. These immune cells are known to express estrogen receptors and have been implicated in the pathogenesis of lupus. This research will advance scientific understanding of why lupus and other autoimmune diseases preferentially affect women. (PAS-07-381)

2. Request for Applications

Autoimmunity Centers of Excellence (ACEs) – The nine ACEs conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials of drugs called immune modulators that act on the immune system. The Centers support close interaction between clinicians and basic researchers to facilitate identification of effective strategies for inducing immune tolerance and developing immune modulation strategies to treat or prevent disease. This interaction also accelerates the translation of scientific advances to the clinic. Completed, ongoing, and

planned clinical trials address lupus, Sjögren's syndrome, rheumatoid arthritis (RA), MS, ulcerative colitis, scleroderma, pemphigus, and type 1 diabetes. The ACEs are currently co-sponsored by the NIDDK and the NIH ORWH. The program will be renewed in FY 2009 with the additional co-sponsorship of the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Neurological Disorders and Stroke (NINDS). More information is available at www.autoimmunitycenters.org. (RFA-AI-08-010)

E. Initiatives on Sex-Based Differences in the Immune Response

1. Request for Applications

Immune Defense Mechanisms at the Mucosa – In January 2008, NIAID held a workshop to discuss recent research advances in immune defense mechanisms at mucosal surfaces, including the female genital tract. NIAID created the initiative "Immune Defense Mechanisms at the Mucosa" to address research gaps identified at the workshop (RFA-AI-08-020).

F. Conferences and Workshops

NIAID Women's Health Research Seminar Series 2008 – The NIAID Women's Health Research Working Group launched its quarterly women's health seminar series in 2008. The goal of the series is to highlight research in infectious and immune-mediated research that advances women's health research. Presentations in 2008 addressed sex differences in HIV and outcomes in HAART; the need for a new strategy to understand how HIV-1 infects women, including the role of the mucosal immune response to HIV in the female genital tract; and sex differences that increase women's risk for lupus and other autoimmune diseases.

Workshop on Advances and Challenges in STI Microbicide Research – This workshop was held in April 2008, in Chapel Hill, North Carolina, to review the ongoing research on microbicides to prevent transmission of sexually transmitted pathogens. The Workshop provided an overview of the opportunities and challenges for STI microbicide research, development, and evaluation. Topics included microbicide safety and clinical trials.

Joint Symposium on HIV Research in Women – CFAR sponsored the first annual University of Washington-University of California at San Francisco Symposium on HIV in women in September 2008 in Seattle, Washington. The purpose of these symposiums is to mutually develop interdisciplinary projects and approaches to research in women, establish standardized definitions for variables pertinent to research in women, and generate synergy between institutions and individuals dedicated to HIV research in women. The theme of the 2008 symposium was "AIDS 2031: Looking Back to Look Forward." More than 100 attendees from a variety of scientific disciplines discussed the need for partnering with the AIDS2031 (www.aids2031.org) group to critically examine the last 25 years of the AIDS epidemic to inform the future research agenda for women. Symposium topics included HIV risk, prevention, and treatment in girls, adolescents, and women; women's participation in biomedical research trials; women's reproductive biology; immunology; and gender differences in HIV and comorbidities.

Workshop on Bacterial Vaginosis: Identifying Research Gaps – NIAID held this Workshop in November 2008, in Bethesda, Maryland, to discuss three areas of research: (1) molecular methods for characterizing the vaginal microbiota, (2) the diagnosis and clinical definitions of bacterial vaginosis, and (3) the role of vaginal bacteria in adverse health events associated with bacterial vaginosis. Attendees participated in an active dialogue that may lead to future collaborations.

Scientific Symposium on Women and AIDS Research – In August 2007, NIAID convened the "Demystifying Women and AIDS Research" symposium at the National Minority Women's Health Summit, which was sponsored by the Secretary's Office on Women's Health. The presenters provided recent research findings on NIAID-sponsored epidemiological, microbicidal, and therapeutics research. More than 100 people attended the symposium, including federal officials, women's health advocates, and health professionals.

The NIAID Division of AIDS (DAIDS) Microbicide Branch Chief Presents at Congressional Briefing on Microbicides Research – NIAID staff participated in a congressional briefing entitled, "Microbicides Research: A Promising HIV/AIDS Prevention Strategy for Women" held in Washington, D.C., in December 2008.

V. Sex/Gender Analysis

NIAID supports research to analyze sex/gender differences in disease susceptibility, pathology, or response to prevention or treatment strategies. The following scientific advances and ongoing and planned activities are highlighted in this report:

VI. Research on Health Disparities among Special Populations

NIAID supports research to understand and eliminate health disparities among special populations including minorities, rural women, lesbians, women of lower socioeconomic status, women with disabilities, etc. The following scientific advances and ongoing and planned activities are highlighted in this report: