NIAID WOMENS HEALTH RESEARCH (FY 2015-2016)

Contents

NIAID WOMENS HEALTH RESEARCH (FY 2015-2016) ........................................................................... 1
Executive Summary ................................................................................................................................. 2
Accomplishments and Activities ......................................................................................................... 3
HIV/AIDS ............................................................................................................................................ 3
Epidemiologic Research ......................................................................................................................... 4
Prevention Research—Topical Microbicides ......................................................................................... 4
Programs to Support the HIV Topical Microbicide Preclinical Pipeline ........................................... 6
Prevention of Mother-to-Child Transmission of HIV ........................................................................... 6
Vaccine Research .................................................................................................................................. 7
Other Prevention Research—HIV Prevention Trials Network (HPTN) .................................................. 7
Therapeutics Research .......................................................................................................................... 9
Infectious Diseases Other than HIV/AIDS ............................................................................................ 11
Malaria .................................................................................................................................................. 11
Zika Virus ............................................................................................................................................ 12
Influenza ................................................................................................................................................ 13
Human Papillomavirus (HPV) .............................................................................................................. 14
Bacterial Vaginosis (BV) ....................................................................................................................... 14
Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) ......................................................................... 14
Tuberculosis (TB) ................................................................................................................................. 15
Fungal Infections ................................................................................................................................. 16
Immunology and Immune-Mediated Diseases ...................................................................................... 16
Immune Response to Vaccinations ....................................................................................................... 16
Immune Changes in Pregnancy ............................................................................................................ 16
Asthma .................................................................................................................................................. 17
Allergy ................................................................................................................................................... 17
Autoimmune Diseases .......................................................................................................................... 18
Systemic Lupus Erythematosus (SLE) ................................................................................................. 18
Multiple Sclerosis (MS) ......................................................................................................................... 19
Rheumatoid Arthritis (RA) .................................................................................................................... 20
The Microbiome and Autoimmunity ..................................................................................................... 20
Systemic Sclerosis (Scleroderma) ......................................................................................................... 20
NIH Strategic Plan for Women’s Health Research ............................................................................... 21
Inclusion .............................................................................................................................................. 21
STEM Career Development Efforts ...................................................................................................... 21
Executive Summary

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to understand, diagnose, prevent, treat, and, ultimately cure infectious and immune-mediated diseases, including diseases 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 other infectious diseases. NIAID also collaborates with other organizations on research initiatives within NIAID's mission areas that aim to improve women's health.

This biennial report provides an overview of selected NIAID-sponsored women's health activities. The first section describes scientific accomplishments and activities in research on HIV/AIDS; non-HIV infectious diseases including sexually transmitted infections (STIs), malaria, influenza, and Zika virus infection; and immunology and immune-mediated diseases such as asthma and allergy. Accomplishments in the area of HIV/AIDS include supporting ongoing clinical trials that test antiretroviral (ARV) drugs and topical microbicides to prevent the transmission of HIV to women or their partners, as well as a clinical trial that showed the effectiveness of a new ARV drug regimen to minimize the risk of mother-to-child transmission of HIV during pregnancy and breastfeeding; development and testing of intravaginal rings containing ARV drugs, including a large clinical trial showing that a vaginal ring helped protect women against sexually transmitted HIV infection; and a major international clinical trial demonstrating that HIV-infected individuals have a considerably lower risk of developing AIDS or other serious illnesses if they start taking ARV drugs as soon as possible upon diagnosis. Other highlights include studies to treat and prevent malaria in pregnant women; promising results of a small clinical trial showing that stem cell transplants may halt the progression of multiple sclerosis (MS); basic and clinical research that could lead to new treatment approaches to minimize the impact of systemic lupus erythematosus (SLE), rheumatoid arthritis, and other autoimmune diseases that disproportionately affect women; improved understanding of how the microbiome may contribute to autoimmune disease; and insights into complications of human pregnancy.

An overview of NIAID activities that address the objectives of the NIH Strategic Plan for Women’s Health Research includes a description of the NIAID Women’s Health Research Working Group. Additional sections provide overviews of NIAID activities to include women in clinical studies, including efforts to increase the enrollment of pregnant women in ethically appropriate clinical research; career development activities; research initiatives; conferences and publications; and research on health disparities in women and special populations.

The research described in this report supports many ORWH Strategic Plan Goals and Objectives, including:

Goal 1.2, Explore sex differences in the structure and function of male and female cells (including stem cells), tissues, organs, and physiological systems.

Goal 1.6, Increase basic and translational research on sex/gender differences in the pathobiology, prevention, and treatment of diseases including HIV/AIDS, urinary tract and sexually transmitted infections. Goal 1.8, Further understanding of sex/gender differences in fundamental mechanisms and patterns of behavioral and social functioning relevant to health and well-being.

Goal 3.3, Encourage research on safe and effective interventions for conditions affecting pregnant women.

Goal 3.9, Examine health disparities among women stemming from differences in such factors as race and ethnicity, socioeconomic status, gender identity, and urban-rural living, as they influence health, health behaviors, and access to screening and therapeutic interventions.
Accomplishments and Activities

HIV/AIDS

The United Nations Joint Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that about 37 million people, including 18 million women, are infected with HIV worldwide. In the United States, 285,000 women are living with HIV. Women face a greater risk of acquiring HIV than men because of substantial mucosal exposure to semen, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners.

Three decades into the HIV/AIDS epidemic, young women bear the brunt of new HIV infections. Globally, adolescent girls and young women (15–24 years of age) are twice as likely to be at risk of HIV infection compared to boys and young men in the same age group. This higher risk of HIV is associated with unsafe and often unwanted and forced sexual activity. Too many young women still struggle to protect themselves against sexual transmission of HIV and to get the treatment they require. This also leaves them particularly vulnerable to tuberculosis (TB)—one of the leading causes of death in low-income countries of women 20–59 years old.

According to WHO, in 2015 women accounted for approximately 50 percent of all adults living with HIV worldwide. The Centers for Disease Control and Prevention (CDC) reported that the rate of new HIV diagnoses in women in the United States declined from 2008 to 2014, and the death rate in U.S. women declined from 2008 to 2013. However, HIV/AIDS and associated diseases and co-infections continue to cause substantial illness and death in the United States and worldwide. In 2013, WHO reported that HIV/AIDS is the leading cause of death globally for women of reproductive age (15-44 years).

In addition to facing complications associated with HIV/AIDS similar to those that affect men, infected women also suffer gender-specific manifestations of HIV disease, including human papillomavirus (HPV)-related cervical dysplasia (abnormal, precancerous cell growth), and cervical cancer. HIV-infected women have a higher prevalence of HPV infection, a higher risk of progression from infection to disease, and an increased risk of invasive cervical cancer and other HPV-related cancers, including anal cancer. Anal cancer is emerging as an important clinical entity in HIV-infected women (as well as in men). And combination ARV therapy for HIV has not significantly decreased the incidence of HPV-related cancers. (Note: For more information on HPV infection, see Infectious Diseases Other than HIV/AIDS.)

Other complications of HIV infection in women, such as recurrent vaginal yeast infections, pelvic inflammatory disease, genital ulcer disease, and severe herpes infections are reduced by successful combination ARV therapy. Drug metabolism differs in women compared with men, potentially resulting in differential responses to ARV therapy and an increased incidence of drug toxicities in women.

In many parts of the world, death and illness due to pregnancy and childbirth are frequent occurrences. Thus, use of contraceptives is the most successful intervention to prevent maternal illness and death, and, by preventing pregnancy, to prevent mother-to-child transmission of HIV. Hormonal methods of birth control are most effective but may interact with antiretroviral drugs, which could lead to additional toxicities or treatment failures. Also, several recent studies have shown an increased risk of HIV transmission to an uninfected male partner if the woman is using hormonal contraceptives. Forms of contraception that are effective, safe, and do not increase the risk of transmitting HIV to an uninfected partner are urgently needed, as are safe and effective methods to prevent mother-to-child transmission of the virus.

Achieving effective treatment of HIV infection may be more problematic for women than for men because women may have difficulty accessing health care and carry a large burden of caring for children and other family members, including those who also may be HIV infected. They often lack social and financial resources to cope with HIV and other challenges.

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

NIAID supports epidemiologic research in the following areas:

- The long-term natural history of HIV infection in women—in particular, research that evaluates the impact of ARV therapy on the clinical course of HIV disease throughout a woman’s life span
- The effect of hormonal, endocrine, bacterial, and local factors on the levels of HIV in the plasma and genital tract, and on sexual transmission of the virus
- 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, including the microenvironment, HIV virology, and immunology of the female genital tract compared with blood

Women's Interagency HIV Study (WIHS)

WIHS is the largest observational study of HIV-infected women and includes participants living in 10 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 highly active antiretroviral therapy (ART). Researchers are investigating factors such as the development of AIDS, drug resistance, co-infections, treatment use and treatment effects, metabolic abnormalities and toxicities, hormonal factors, aging, neurocognitive functioning, and physical impairment. This study has led to a better understanding of how HIV is spread, how HIV disease progresses, and how it can best be treated. More information is available at http://statepiaps.jhsph.edu/wihs.

International Epidemiology Databases to Evaluate AIDS (IeDEA)

The IeDEA consortium brings together clinical data collected as part of research initiatives and diverse care programs. Seven global regions enroll nearly 1 million patients who are representative of the HIV epidemic within their region. The North American AIDS Collaboration of Observational Research Databases includes data from more than 21,000 women living in the United States or Canada. The consortium’s size allows for in-depth assessment of clinical outcomes, including rare events and their predictors. Globally, IeDEA represents the severity of the epidemic among women, with more than half of the data coming from women. More information is available at www.iedea.org.

Science Advances

Lung Cancer Incidence and Survival Among HIV-Infected and Uninfected Women and Men. Lung cancer incidence is significantly higher among HIV-infected individuals than in the general population, yet the precise role of HIV and immune suppression in this phenomenon remains somewhat elusive. Researchers determined the lung cancer incidence and survival time among HIV-infected and uninfected women and men in the cohorts of the WIHS and the Multicenter AIDS Cohort Study (MACS). Overall, the lung cancer incidence rate was significantly higher among women than men, and higher among HIV-infected participants than among uninfected participants. The study found that HIV infection alone was not an independent risk factor for lung cancer, but that the amount of cigarette smoking over time, and prior AIDS pneumonia among HIV-infected adults, were major contributors for the development of lung cancer. (Hessol et al., 2015. PMID 25888645)

Prevention Research—Topical Microbicides

There is an urgent need to develop a safe, effective, and acceptable topically applied chemical and/or biologic barrier to prevent sexually transmitted HIV infection. NIAID-sponsored research focuses on the development of topical microbicides that: (1) prevent HIV infection and/or viral replication, (2) are safe and do not irritate vaginal, cervical, urethral, or rectal tissues, and (3) reduce HIV transmission and acquisition, even in the presence of other STIs, which increase the risk of acquiring HIV.
Microbicide Trials Network (MTN)

In 2006, the MTN was formed to develop and evaluate microbicide products aimed at reducing the sexual transmission of HIV. MTN consists of a robust network of expert scientists and investigators, with U.S. and international clinical research sites. The network uses a focused research and development strategy to advance the most promising microbicides toward licensure for prevention of HIV acquisition and transmission. More information is available at [http://www.mtnstopshiv.org](http://www.mtnstopshiv.org).

Clinical Trials

**Vaginal Ring Infused with Antiretroviral Drug Confers Partial Protection from HIV Infection.** The MTN-020/ASPIRE study (A Study to Prevent Infection with a Ring for Extended Use) examined whether a vaginal ring that continuously releases dapivirine, an experimental antiretroviral drug, could protect against HIV infection among women. This study, funded by NIAID, NIMH, and NICHD, enrolled 2,629 women ages 18–45 years in Malawi, South Africa, Uganda, and Zimbabwe. Study participants received a vaginal ring that was replaced every 4 weeks and contained either dapivirine or placebo. All participants also received HIV prevention services, including counseling about how to protect against HIV infection, and free condoms. Two study sites reported such low adherence to the ring protocol—missing follow-up appointments and using the ring inconsistently—that the data gathered from these sites were removed. Without these sites, the dapivirine vaginal ring (DPV VR) reduced the risk of HIV infection by 37 percent among all women. The effect was markedly different according to the age of participants. In women ages 25 and older, the ring lowered the risk of HIV by 61 percent, but the ring provided no protection for 18–21-year-olds. This disparity between age groups could be related to lower adherence to ring use or age-related biological differences in susceptibility to HIV infection. Overall, the results indicate that a DPV VR could offer many women an option, in addition to oral pre-exposure prophylaxis (PrEP), to protect against HIV infection. (Baeten et al., 2016. [PMID 26900902](https://www.ncbi.nlm.nih.gov/pubmed/26900902))

**Adherence to Use of Rectal Microbicide Gel.** MTN-017, a phase II multi-country study, examined the safety and acceptability of the reduced glycerin tenofovir 1% gel in men who have sex with men and transgender women. As reported in February 2016, this study demonstrated for the first time that the rectal microbicide was safe for extended use. Further analysis showed that participants were just as likely to follow through with use of an anti-HIV gel with anal sex as they were to use daily PrEP. (Cranston et al., 2016; [Conference on Retroviruses and Opportunistic Infections](https://www.conferenceonravi.org/); Carballo-Diéguez et al., 2016; 2016 [HIV Research for Prevention Conference](https://www.internationalaidsconf.org/))

**Open Label Study of Vaginal Ring for HIV Prevention.** The HIV Open-label Prevention Extension (HOPE) or MTN-025 study will build on the results of the ASPIRE study by gathering additional information on the safety of the DPV VR. How would women use the ring, knowing that it can help reduce their risk of HIV; and the relationship between adherence and HIV protection. The study also seeks to understand why the ring may work well for some women but not for others. The DPV VR is meant to be used for a month at a time; women can insert and remove it themselves.

**Assessment of ASPIRE and HOPE Adherence.** The first phase of the MTN-032 study will assess 224 participants with varying levels of adherence to the DPV VR in the ASPIRE study. ASPIRE participants will be preselected and approached for study participation based on their plasma dapivirine levels and residual drug levels from returned vaginal rings. Participants will be asked to complete a single in-depth interview or a focus group discussion to examine factors influencing adherence. The second phase of the study will examine the motivation for participation in the study and for use of the DPV VR in HOPE study participants with various levels of adherence.

The DPV VR is being evaluated in other populations of potential users, should it become a licensed product, in collaboration with International Partnership for Microbicides (IPM, [http://www.ipmglobal.org/](http://www.ipmglobal.org/)).

- **MTN-024/IPM 031**, a phase Ia multisite trial that enrolled and randomized 96 postmenopausal U.S. women, demonstrated that the DPV VR was safe and well tolerated when inserted monthly for a 12-week period.
- **MTN-023/IPM 030**, a phase Ia study to evaluate the safety, acceptability of, and adherence to the DPV VR among adolescent girls in the United States, was recently completed. The study enrolled and randomized 96 healthy, HIV-uninfected adolescent girls (ages 15-17 years) to receive either a DPV VR or a placebo vaginal ring, which was inserted once every 4 weeks over a 24-week period. Data analysis is ongoing.
• **MTN-029/IPM 039**, a phase I open-label, multisite study designed to assess the presence of dapivirine in breast milk when lactating women use the DPV VR for 14 days, is ongoing. The trial will also evaluate safety, tolerability, and adherence to the ring among these 16 U.S. women.

**Programs to Support the HIV Topical Microbicide Preclinical Pipeline**

The development of new topical microbicide products continued in 2015–2016 and was supported by programs designed to create a sustainable pipeline of topical microbicide products, strategies, and technologies supporting microbicide safety and efficacy testing. The first program, the Prevention Innovation Program (PIP), supports innovative, high-risk research to develop microbicide products and delivery systems. Three new PIP awards use nanotechnology-based approaches to develop new drug delivery system strategies for sustained release of topical microbicides.

The second program, the Integrated Preclinical Clinical Program (IPCP) for Microbicides and Biomedical Prevention, supports preclinical and first-in-human clinical trials to advance candidate microbicides to clinical testing. A new IPCP award is supporting the development of sustained release vaginal films containing the HIV integrase inhibitor MK 2048, an ARV drug. In addition, two safety and pharmacokinetic studies of combination intravaginal rings containing two ARVs, MK-2048 and vicriviroc, a CCR5 receptor antagonist, were initiated.

Lastly, NIAID issued a funding opportunity announcement to support innovative biomedical and proof-of-concept research to understand how reproductive maturation or injury alters the mucosal environments at HIV-susceptible sites. This information is essential to providing the safest and most efficacious biomedical prevention strategies, including topical microbicides.

**Science Advance**

**Rectal Safety, Acceptability, Pharmacokinetic and Pharmacodynamic Study of Tenofovir 1% Gel.**

The CHARM-01 study characterized three tenofovir gels for rectal application: a new rectal-specific formulation, a vaginal formulation (used in the CAPRISA 004 and VOICE vaginal phase IIb trials and RMP-02/MTN-006 phase I rectal safety study) and a reduced-glycerin vaginal formulation gel (used in the MTN-007 phase I and MTN-017 phase II rectal microbicide trials). All three formulations were found to be safe and acceptable. Use of all gels was associated with significant inhibition of HIV infection of biopsied tissue (McGowan et al., 2015. PMID 25942472)

**Prevention of Mother-to-Child Transmission 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 of this mother-to-child-transmission (MTCT) occurs late in pregnancy or during birth. Currently, the United Nations Children's Fund (UNICEF) and WHO recommend that infants born to HIV-infected mothers be exclusively breast-fed for at least 12 months. NIAID is conducting studies for prevention of mother-to-child transmission (PMTCT) in HIV-infected pregnant women. NIAID-sponsored PMTCT research focuses on the following goals:

- Define 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.
- Develop and test strategies for PMTCT of HIV infection through clinical trials in the United States and international settings.
- Develop interventions for PMTCT of HIV via breast milk.

**The International Maternal Pediatric Adolescent AIDS Clinical Trials Group**

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), sponsored by NIAID and NICHD, is a network dedicated to significantly decreasing the mortality and illness associated with HIV disease in children, adolescents, and pregnant women. IMPAACT develops and evaluates safe, cost-effective approaches for interrupting mother-to-infant HIV transmission; evaluates treatments for HIV-infected children, adolescents, and pregnant women; investigates strategies for treating and preventing co-infections and illnesses associated with HIV; and evaluates vaccines for preventing HIV sexual transmission among adolescents. More information is available at https://impaactgroup.org/
Postpartum HIV Superinfection Is Not Associated With Mother-to-Child Transmission Through Breastfeeding. HIV superinfection occurs when a person with HIV is infected with a new strain of HIV. This can increase viral load (blood levels of HIV) and the risk of HIV transmission to other people. To examine whether maternal HIV superinfection affects the risk of MTCT of HIV through breastfeeding, NIAID intramural researchers further analyzed data from the Post-Exposure Prophylaxis of Infants trial in Malawi. Maternal HIV superinfection did not increase the odds of MTCT of HIV via breastfeeding when the researchers considered maternal age, baseline CD4+ cell count, and baseline viral load. Longer breastfeeding duration was associated with a lower risk of HIV superinfection. The high rates of superinfection observed in this study support the use of ART during pregnancy and for a lifetime thereafter, as it is likely to reduce the risk of MTCT and potential adverse effects of HIV superinfection (Redd et al., 2015. PMID 26244396).

Clinical Trial

Promoting Maternal-Infant Survival Everywhere (PROMISE) Study. This large, multinational clinical trial, begun in 2010, was designed to determine how best to reduce MTCT during pregnancy and breastfeeding and preserve maternal health during and after pregnancy and breastfeeding. Study participants were recruited from 12 countries whose levels of resources range from high to low. The study concluded that there was a significantly lower rate of MTCT during the period before childbirth among those women who received a three-drug combination, and treatment with a combination containing the drug lamivudine resulted in fewer infant deaths in the first 2 weeks of life and fewer very premature deliveries compared to treatment with another triple-drug combination. The study also found that for HIV-infected women in good immune health, taking a three-drug regimen during pregnancy prevents MTCT more effectively than taking one drug during pregnancy, another during labor, and two more after giving birth. The findings were reported during a scheduled interim review and support the recommendation by the WHO and most countries to provide a three-drug regimen to all pregnant women with HIV infection.

Vaccine Research

Vaccines are the foundation of preventive measures to curtail infectious disease epidemics. NIAID is committed to supporting basic, translational, and clinical research to develop a safe and effective vaccine to prevent HIV/AIDS, including ongoing clinical trials of promising vaccine strategies. NIAID is part of a public-private collaboration that aims to build on the landmark NIAID-funded RV144 vaccine trial, which showed for the first time that an investigational vaccine could confer a modest degree of protection against HIV infection in humans. In addition, NIAID is working to develop novel methods, such as broadly neutralizing antibodies, to prevent HIV infection.

HIV Vaccine Trials Network (HVTN)

The HVTN is an international collaboration of scientists searching for an effective and safe HIV vaccine. HVTN's mission is to facilitate the process of testing preventive vaccines against HIV/AIDS, conducting all phases of clinical trials, from evaluating experimental vaccines for safety and the ability to stimulate immune responses to testing vaccine efficacy. Studies conducted by HVTN enroll both men and women and data are analyzed for gender differences with regard to safety, tolerability, and immune responses. In a number of studies, the HVTN collects and analyzes mucosal secretions and tissue samples from the vagina and rectum to evaluate immune responses induced by a vaccine or broadly neutralizing monoclonal antibody. More information is available at [http://www.hvtn.org](http://www.hvtn.org).

Clinical Trials

Early-Phase Clinical Trial Shows Investigational HIV Vaccine is Safe and Immunogenic. A recent phase I/II clinical trial (HVTN 100) in South Africa evaluated an investigational HIV vaccine regimen designed to improve upon the RV144 regimen. Early data from this trial show that the improved vaccine is safe and induces an immune response against the virus. NIAID has initiated a phase IIb/III clinical trial to further evaluate the vaccine’s efficacy. Even a partially effective HIV vaccine could have a significant positive impact on the health of women, particularly in resource-limited settings.

Other Prevention Research—HIV Prevention Trials Network (HPTN)

Established in 2000, HPTN is a worldwide collaborative clinical trials network that develops and tests the safety and efficacy of primarily non-vaccine prevention strategies. The HPTN research agenda focuses on the use of ARV
therapy; treatment and prevention of STIs; treatment of substance abuse, particularly injection drug use; behavioral risk reduction interventions; and integrated combination strategies to reduce HIV transmission and acquisition. HPTN studies are conducted in various populations, including women, and in geographical regions that bear a disproportionate burden of HIV infection. More information on HPTN is available at http://www.hptn.org.

Clinical Trials

**Young South African Women Can Adhere to Daily PrEP Regimen.** The ADAPT Study (HPTN 067) found that young, single black women in South Africa adhered to a daily pill regimen to prevent HIV infection—an HIV prevention strategy known as pre-exposure prophylaxis, or PrEP. The study involved 179 women with a median age of 26 in Cape Town, South Africa; 179 black men who have sex with men (MSM) and transgender women (TGW) in Harlem, New York; and 178 MSM and TGW in Bangkok, Thailand. Those enrolled in this open-label study were educated about the efficacy of daily PrEP and knew that they were taking active drugs rather than placebo. Although some previous placebo-controlled PrEP clinical trials in women in sub-Saharan Africa had found challenges with adherence, 76 percent of women assigned to take PrEP on a daily basis in the study adhered to the prescribed regimen. (The MSM and TGW from Harlem and Bangkok who participated in the study adhered to the daily regimen 65 percent and 85 percent of the time, respectively.)

Following completion of the study, a subset of the South African women participated in a qualitative sub-study including focus groups and in-depth interviews. Among these women, PrEP use was heavily influenced by underlying beliefs about the safety of PrEP, a desire to contribute something positive to one’s community, and trust in transparency and integrity of the research. The researchers propose a framework that could inform future intervention trials and implementation of PrEP programs. (Amico et al., 2016. PMID 27317411)

**Maraviroc-Containing Regimen found Safe for HIV Prevention.** HPTN 069/ACTG 5305, a phase II study, evaluated the safety and tolerability of adding the ARV drug maraviroc to drug combinations taken daily as PrEP by MSM and women at increased risk for acquiring HIV. The study findings indicate that maraviroc-containing regimens were as safe and well-tolerated as the Food and Drug Administration (FDA)-approved form of PrEP, a combination of tenofovir and emtricitabine also known as Truvada (Gulick et al., 2016; CROI).

**Study Finds PrEP Use Feasible Among High-Risk Groups in U.S. Community Settings.** A study called the PrEP Demonstration Project found that a majority of MSM and transgender women at high risk for HIV infection took anti-HIV medications most of the time. The study findings lend support to the feasibility and potential clinical benefit of this strategy for HIV prevention in community settings (Liu et al., 2015, International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention).

**Long-Acting Injectable Agent for HIV Prevention.** Researchers conducted a phase IIa study to evaluate the safety, tolerability, pharmacokinetics, and acceptability of a long-acting injectable agent, GSK1265744 (cabotegravir), in healthy, HIV-uninfected men and women (HPTN 077).

**Antibody-Mediated Prevention Studies.** Two phase IIb studies are currently examining whether intravenous infusions of the broadly neutralizing anti-HIV antibody VRC01 are safe and effective at preventing HIV infection. The first study, HVTN 703/HPTN 081, will enroll 1,500 sexually active women in Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania and Zimbabwe. The antibody will be delivered as an intravenous infusion every 8 weeks. The study will also examine the levels of antibody in the blood of study participants who receive different amounts or doses of the antibody. The second study, HVTN 704/HPTN 085, will evaluate antibody-mediated prevention among men and transgender men and women who have sex with men. More information is available at: http://ampstudy.org.

**Oral PrEP in Young African Women.** HPTN 082 is a sub-Saharan-based research study designed to assess the number and characteristics of young women who accept versus decline PrEP at enrollment. The study will also compare adherence to PrEP between women who are randomized to receive standard adherence support and those receiving enhanced adherence support.

**Population Effects of ART to Reduce HIV Transmission (PopART).** The PopART/HPTN 071 study is exploring whether providing a package of HIV prevention strategies can reduce HIV transmission at a population level. These prevention interventions include universal household voluntary HIV counseling and testing, linkage of HIV infected individuals to care, and early initiation of ART for all those testing HIV positive. The study is being conducted in 21 communities in the Western Cape of South Africa, and in Zambia.
Detecting HIV Using Self-Administered Vaginal Swabs. The HVTN 915 study, which completed follow-up visits in 2015, was an observational study that followed 50 South African women to evaluate whether HIV exposure can be detected in daily vaginal swabs after episodes of unprotected sex. Using a mobile phone-based application, the study investigators sought to correlate data on sexual behavior with vaginal swab samples collected by the clinicians and participants. The study found that cellphone surveys appear to be a viable method to collect risk behavior information.

Therapeutics Research

AIDS Clinical Trials Group (ACTG)

Established in 1987, ACTG is a multicenter clinical trials network that conducts translational and therapeutics research in the United States and internationally. Research priorities include translational research and optimization of the clinical management of HIV/AIDS, including HIV-related co-infections and diseases. In collaboration with other clinical trials networks, ACTG also pursues research and development of therapeutic vaccines and research on HIV treatment in pregnant women. More information is available at http://actnetwork.org.

Centers for AIDS Research (CFAR)

CFAR is a unique trans-NIH program that provides infrastructure to support interdisciplinary, 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 easily be funded by other mechanisms. There are currently 18 CFARs at academic and research institutions throughout the United States. Several of them are actively supporting research activities in women. In 2015–2016, 12 CFARs supported more than 20 women’s health pilot projects through the CFAR Developmental Cores. In addition, the Inter-CFAR Collaboration on HIV Research in Women is a network of CFAR investigators dedicated to promoting cutting-edge HIV research in women. The collaboration develops new strategies for future research to address HIV-related issues unique to women and promotes career development and professional growth among junior investigators interested in this field. Finally, the Harvard CFAR has a scientific working group that focuses on safer conception and contraception for HIV-infected persons in resource-limited settings. More information on CFAR is available at https://www.niaid.nih.gov/research/centers-aids-research.

Science Advances

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. A major international randomized clinical trial known as the Strategic Timing of AntiRetroviral Treatment (START) study found that HIV-infected individuals have a considerably lower risk of developing AIDS or other serious illnesses if they start taking antiretroviral drugs sooner, when their CD4+ T-cell count is higher, instead of waiting until the CD4+ cell count drops to lower levels. The START study was conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) at 215 sites in 35 countries. The trial enrolled 4,685 HIV-infected men and women who had never taken ART and had CD4+ cell counts in the normal range—above 500 cells per cubic millimeter (cells/mm3). Approximately half of the study participants were randomized to initiate ART immediately (early treatment), and the other half were randomized to defer treatment until their CD4+ cell count declined to 350 cells/mm3. Previous evidence to support early treatment among HIV-positive people with CD4+ cell counts above 350 was limited to data from non-randomized or observational studies, and expert opinion. The START study is the first large-scale randomized clinical trial to establish that earlier ART benefits all HIV-infected individuals. The 2015 results were rapidly reflected in the updated WHO guidelines, which recommend immediate treatment of anyone infected with HIV. (The INSIGHT START Study Group, 2015. PMID 26192873)

Understanding Sex-Specific Differences in HIV Disease. HIV-infected women tend to have lower levels of the virus in their blood compared with men both before and after starting ART. Yet HIV disease progresses at the same rate or faster in women than in men. To investigate possible reasons for these sex-specific differences, researchers looked at markers of immune activation and inflammation in 215 HIV-infected, treatment-naïve men and women who participated in the NIAID-funded multinational Prospective Evaluation of Antiretrovirals in Resource-Limited Settings trial. The investigators found that, with treatment, women had greater increases in their CD4+ T-cell counts, and either greater increases or less reduction in various key markers of inflammation and immune activation compared with men. These findings suggest that women experience less reduction in immune activation and
inflammation than men in response to ART. Further studies are needed to investigate how this relates to the worse HIV-related outcomes in women. (Mathad et al., 2016. PMID 27258230)

**Virus Reactivation, Immune Activation, and ART in HIV-Positive Women.** NIAID intramural investigators examined the expression of vaginal inflammation-promoting factors called cytokines in HIV-infected women before and after initiation of ART. Initiation of ART can lead to a short-term increase of herpes virus-related illnesses including varicella-zoster virus infection, increased cytomegalovirus (CMV) retinitis, herpetic genital ulcers, and rare occurrences of herpes simplex virus (HSV)-associated encephalitis. The association of viral shedding with higher levels of the cytokine interleukin-6 suggests that HSV reactivation may play a role in immune activation after ART initiation. (Nason et al., 2016. PMID 27191006)

**Sex Differences in Response to the First-Line HIV Drug Atazanavir.** The first-line HIV therapy atazanavir is commonly used in combination ART regimens because it is a potent, once-daily drug that patients tolerate well. Prior studies have shown sex-related variability in blood concentrations of atazanavir. How the body processes the drug over time and the resulting clinical implications had not been determined. NIAID-funded researchers studied atazanavir concentration in the blood of 131 women and 655 men infected with HIV. They found that women cleared atazanavir from their blood 14 percent more slowly compared with men, after accounting for differences in body weight. In addition, women with fast clearance of atazanavir and men with slow clearance had worse clinical outcomes, including an inability to tolerate atazanavir and failure to suppress HIV. These outcomes occurred despite patients’ adherence to atazanavir treatment. This study showed that a patient’s sex is an important factor in atazanavir clearance and treatment outcomes. (Venuto et al., 2014. PMID 25159623)

**HIV Infection Has a Small but Negative Effect on Cognitive Function in Women.** Although several studies have reported cognitive impairment in women infected with HIV, previous studies were too small to understand the factors that may affect cognitive function in these women. As part of the NIAID-funded WIHS, the largest and longest-running study to investigate the impact of HIV on U.S. women, researchers studied cognitive function in American, urban-dwelling women. To distinguish the effects of HIV from other factors that could affect cognitive function, the researchers studied socially and demographically similar women who were either HIV-infected or uninfected. The results showed that HIV infection had a very small but significant effect on cognition. HIV-infected women performed worse than uninfected women on tests of verbal learning, delayed recall and recognition, attention, and psychomotor speed (coordinating thinking and physical movement). The factor most strongly associated with cognitive deficit in HIV-infected women was low reading level. HIV-infected women with low education or compromised immune functions were most vulnerable to cognitive deficits. Results of this study will help define how best to treat HIV-infected women in the United States and globally. (Maki et al., 2015. PMID 25540304)

**Analysis Reflects HIV Treatment Practices and Behaviors in Washington, DC.** To identify factors that could help HIV-positive women achieve long-term suppression of the virus and reduce HIV transmission, scientists funded by NIAID analyzed data from 329 HIV-positive women living in Washington, DC, who participated in four or more visits as part of the DC WIHS between 1994 and 2012. The researchers characterized three distinct patient populations: approximately 40 percent of women had a high probability of being non-suppressed and viremic (having virus in the bloodstream) at each visit, a second group (35.6 percent) had a moderate risk of intermittent viremia, and a third group (27.3 percent) had a low risk of viremia during study follow-up. The women in the group with a high risk of viremia were most likely to succumb to HIV/AIDS, with a 31 percent mortality rate. Women in the group at moderate or low risk of viremia on follow-up did not have significantly different mortality rates, at 6.9 and 4.7 percent, respectively. Despite the availability of ART, only one-third of the women in the study maintained consistently low virus levels. DC WIHS is a community-based study and the findings likely reflect the characteristics and behaviors of participants in the Washington, DC, area and thus regional treatment successes and failures. The study highlights gaps in the success of treatment programs to fully suppress HIV and suggests that more tailored interventions may be needed to reduce HIV transmission, prevent the emergence of drug resistance, and improve outcomes of community HIV treatment programs. (Ocampo et al., 2015. PMID 26695971)

**Untreated HIV Infection Has No Association with Low Bone Mineral Density (BMD).** HIV infection is associated with osteoporosis, a reduction of BMD that leaves bones vulnerable to breaking under mild stress, such as coughing or bending over. In people over 50, women are four times more likely than men to have osteoporosis. The contribution of untreated HIV infection to BMD loss is unclear. NIAID-funded investigators examined the association of traditional osteoporosis risk factors and HIV parameters with BMD at the hip and spine in HIV-infected adults who had normal CD4+ cell counts and had not undergone ART. The START Bone Mineral Density
Substudy involved 424 ethnically diverse participants in 11 countries. Although osteoporosis among the participants was rare (1.9 percent), low BMD was common (35.1 percent). A longer duration of HIV infection (time since HIV diagnosis) was associated with lower BMD at the hip, but not the spine. The scientists found that low BMD was associated with traditional risk factors such as female sex and older age but not with CD4+ cell count or viral load, which are markers of HIV/AIDS severity. This is the first study to evaluate BMD in untreated HIV-infected adults across more than one region. (Carr et al., 2015. PMID 25711332)

**Antiherpes Drug’s Role in Decreased Viral Load and Disease Progression in HIV-Positive Women.** NIAID intramural investigators published results from a clinical trial (NCT00405821) of the anti-herpes drug acyclovir in HIV-positive women, which sought to determine changes in immune activation due to the drug. Study data suggest that decreased monocyte activation may play a minor role in the ability of daily acyclovir use to slow HIV disease progression (Redd et al., 2015. PMID 25904747).

**Clinical Trials**

**Promoting Maternal-Infant Survival Everywhere (PROMISE) Study.** Some of the maternal health components of this study (described above) are being conducted in settings where highly active ART is the standard of care during pregnancy and women do not typically breastfeed. This maternal health component is seeking to determine the best strategy for treating infected new mothers who have not progressed to AIDS.

**The Effect of Vitamin D Repletion on Postmenopausal Women with HIV.** This study (ClinicalTrials.gov NCT01375010) examined the effects of vitamin D supplementation on bone turnover, rates of bone loss, and indices of immune function in HIV-infected postmenopausal African-American and Hispanic women. Previous research revealed that low vitamin D levels are common in this population. The study followed 83 women to determine the change in BMD over one year. As other research has suggested that HIV-positive women have higher rates of bone loss than HIV-negative women, vitamin D therapy may help prevent complications of bone loss, particularly bone fractures. Data are currently being analyzed.

**Evaluating Pharmacokinetic Interactions with Vaginal Ring Contraceptives and ART.** This study is evaluating whether the ARVs efavirenz and atazanavir/ritonavir affect the hormones released by a birth control method called NuvaRing. Some studies have shown that ARV drugs interact with the hormones released by some birth control medication. These interactions may cause the birth control drug to be less effective at preventing pregnancy, and may increase the spread of HIV to others. The results of this study will ultimately inform whether NuvaRing is safe and effective for women with HIV infection who are taking ARVs. The study will also examine the hormone levels in HIV-infected women who will use the NuvaRing but not ARVs. (A5316, Enrolling)

**Infectious Diseases Other than HIV/AIDS**

Many infectious diseases, including malaria and STIs such as human papillomavirus (HPV), are critical global and national health priorities. These diseases can have a devastating impact on women, with the potential for causing long-term health problems. For example, many diseases can cause pregnancy loss at any stage, problems with the development of the fetus, or complications for the newborn.

**Malaria**

The parasite *Plasmodium falciparum* is the deadliest and most common malaria-causing species in Africa. Malaria infection during pregnancy has substantial risks for the pregnant woman, her fetus, and the newborn child.

**Science Advances**

**New Vaccine Targets for Pregnancy-Associated Malaria.** The *P. falciparum* protein VAR2CSA is a promising target for vaccine development against pregnancy-related malaria. This protein is expressed on the surface of infected red blood cells and binds to the placenta. NIAID-funded researchers studied fragments of VAR2CSA to determine which part of the protein is targeted in women who have acquired natural immunity after pregnancy and thus identify new targets for a vaccine against pregnancy-associated malaria. In a trial conducted in Mali, researchers measured the reactivity of serum collected from men, women, and children to five different fragments of VAR2CSA. They found that serum from malaria-exposed women with a history of at least one pregnancy reacted more strongly to two of the five VAR2CSA fragments than did serum from men, children, and women who had never been pregnant. In addition, a greater number of pregnancies was associated with stronger reactivity to the two
fragments. This finding is consistent with previous observations that with each pregnancy, women exposed to *P. falciparum* develop more antibodies that protect against the parasite and are associated with better birth outcomes. This study provides insight into how natural immunity to pregnancy-associated malaria is acquired and could inform the development of a vaccine. (Travassos et al., 2015. PMID 25918203)

**Additional Insights into Pregnancy-Associated Malaria Vaccine Development.** Pregnant women are highly susceptible to malaria, particularly during their first pregnancy. Red blood cells that are infected by the malaria parasite *P. falciparum* concentrate in the placenta, leading to serious consequences such as severe anemia in the pregnant woman, stillbirth, low birth weight, or death of the newborn. Immunity from infection may be mediated in part by antibodies against VAR2CSA that block adhesion of the infected blood cells to the placenta. Studies suggest that women who have been pregnant multiple times acquire a repertoire of naturally occurring antibodies against VAR2CSA, and VAR2CSA is considered a prime vaccine candidate against placental malaria. NIAID intramural researchers used a new approach to assess domains, or regions, of VAR2CSA that are recognized by naturally acquired antibodies. They found that the broadly neutralizing antibodies in women who have had multiple pregnancies did not strictly recognize the type of VAR2CSA domains used in the study, suggesting that development of vaccines based on isolated VAR2CSA domains might induce antibodies with only limited broadly neutralizing activity. (Doritchamou et al., 2016. PMID 27190180)

**Mouse Model Mimics Human Malaria Infection During Pregnancy.** Malaria infection during pregnancy can have severe consequences, such as severe anemia in the pregnant woman, stillbirth, low birth weight, and even death of the newborn. To better understand this disease during pregnancy, NIAID scientists established a new malaria pregnancy model in mice that mimics two processes common to humans during pregnancy: 1) re-emergence of a prior malaria infection and 2) infection with a new strain of malaria parasite following a pre-pregnancy infection with another strain. These infections resulted in a variety of symptoms, including anemia and elevated levels of inflammation-causing factors called cytokines in the pregnant mouse, still births and deaths of newborn mice, and lower weight and altered susceptibility to future infection in the offspring. Many of these symptoms mimic the human condition, suggesting that this mouse model will be useful for studying the mechanisms underlying malaria infection during pregnancy. (Sharma A, Conteh S, Langhorne J, & Duffy PE, 2016. PMID 27467392)

**Clinical Study**

NIAID intramural scientists have established the Pregnancy Malaria Immunology, Pathogenesis, and Vaccine Development initiative. Clinical and laboratory investigations for this project aim to determine factors associated with malaria in pregnant women and young children. These studies are informing intramural scientists’ efforts to develop a pregnancy-associated malaria vaccine.

**Clinical Trial**

**Host and Parasite Factors That Influence Susceptibility to Malaria Infection and Disease During Pregnancy and Early Childhood in Ouelessebougou and Bamako, Mali (NCT01168271).** Researchers are conducting a longitudinal cohort study in Ouelessebougou, Mali, an area of intense seasonal malaria transmission. Up to 2000 pregnant women and their infants and 2000 children ages 0–3 years will be enrolled and infants and children will be followed to age 5, with clinical evaluation and periodic blood samples obtained. In addition, 2000 children up to age 10 who have fevers will be enrolled at district health centers or a pediatric hospital, and samples will be obtained and evaluated. Finally, 500 pregnant women will be enrolled for a case-control study on pregnancy malaria and preeclampsia (hypertension occurring in pregnancy). Researchers will analyze various endpoints to determine parasite and host (human) factors that are associated with infection and disease in pregnant woman and young children.

**Zika Virus**

Zika virus is a mosquito-borne virus that can be sexually transmitted and causes serious birth defects, including microcephaly, in babies born to mothers infected with the virus during pregnancy. Microcephaly is a condition marked by an unusually small head, brain damage, and developmental delays. Zika virus infection has been associated with other fetal development problems, including eye defects, hearing loss, and impaired growth. Most people who are infected with Zika virus do not become sick. However, Zika virus can persist in the body for several weeks after infection, even in a person without symptoms. There is no medicine or vaccine to treat or prevent Zika virus infection.
Nonhuman Primate Model Shows Effects of Zika Infection on Developing Brain. Studies to test the relationship between fetal brain injury and Zika virus infection during pregnancy were previously hampered due to the lack of an animal model that closely mirrors Zika infection and fetal brain development in humans. To address this issue, researchers studied Zika infection in nonhuman primates that have a placental structure and timing of fetal brain development similar to that of humans. They infected pregnant pigtail macaque monkeys with Zika virus at a time equivalent to the third trimester of human pregnancy, tracked fetal development after infection via sonograms and magnetic resonance imaging (MRI), and performed autopsies at a time equivalent to 38 weeks of human pregnancy to evaluate brain development and invasion of the Zika virus into the fetal brain. The researchers found a pattern of virus invasion of the brain and associated brain developmental abnormalities similar to that observed in humans. The results provided the first direct evidence that Zika virus can cross the placental barrier late in pregnancy and impair fetal brain development. The findings underscore the need for rapid treatment or preventive measures after a mosquito bite. Researchers hope that this animal model may serve as a valuable tool to test possible vaccines and treatments against the potentially serious effects of Zika infection on the developing fetus. (Adams Waldorf et al., 2016. PMID 27618651)

Clinical Study

Zika in Infancy and Pregnancy (ZIP) (NCT02856984). In June 2016, NIAID and other NIH Institutes launched the Zika in Infants and Pregnancy (ZIP) trial. The study aims to enroll as many as 10,000 pregnant women at up to 15 sites where Zika virus is prevalent. Participants will enroll in their first trimester of pregnancy and will be followed throughout their pregnancies to determine if they become infected with Zika virus and if so, the outcomes for both mother and child. The participants’ infants will be carefully followed for at least one year after birth.

Influenza

Influenza virus causes an acute respiratory infection in humans by entering and replicating in lung cells. Each year, seasonal influenza kills between 3,000 and 49,000 Americans and hospitalizes as many as 200,000. Pandemic influenza can produce even greater devastation.

Science Advances

Estrogen Provides Women, but Not Men, Enhanced Protection Against Influenza. Young women with influenza virus infections have more severe outcomes when compared with men of the same age. Since the severity of infection in females changes with respect to age and during pregnancy, it is thought that hormones are responsible for sex-specific differences in response to influenza. To investigate these differences, researchers infected human nasal epithelial cell cultures with a seasonal influenza strain and studied how the infected cells responded to the female hormone estrogen, or to chemicals, termed estrogenic compounds, that mimic estrogen. Treatment of nasal cells with estrogen or estrogenic compounds reduced influenza virus replication, lowered virus levels, and dampened cell metabolic processes in cells isolated from female, but not male, donors. Together, these results demonstrate that estrogen and estrogenic compounds have antiviral properties and can control cellular function in tissues outside the reproductive tract, suggesting that FDA-approved estrogenic drugs could be used to help treat influenza virus infections in women. (Peretz, Pekosz, Lane, & Klein, 2016. PMID 26684252)

Progesterone Protects Female Mice Against Influenza Infection. Progesterone is a female hormone present in contraceptives used by more than 100 million women worldwide, and is known to have anti-inflammatory effects in the reproductive tract. But the role of progesterone in viral infections outside the reproductive tract is an open question. To investigate this question, scientists asked whether progesterone has any effect on influenza A virus (IAV) infection in mice. Mice that had had their ovaries removed to deplete progesterone received either progesterone or placebo, and were subsequently infected with IAV. The progesterone-treated mice had less inflammation and tissue damage in the lungs, better lung function, and more rapid repair of inflammatory damage to the lung cells compared with mice that received placebo. Progesterone treatment elevated the number of immune cells known as T-helper cells and increased the levels of a growth factor called amphiregulin (AREG). Progesterone treatment of mechanically damaged lung tissue also increased expression of AREG and enhanced wound repair. These findings suggest that progesterone stimulates tissue repair in the respiratory tract following influenza infection and show that sex hormones have notable health effects beyond the reproductive tract. (Hall et al., 2016. PMID 27631986)
Human Papillomavirus (HPV)

HPV is the most common STI. Persistent infection with certain strains of HPV can lead to cervical cancer, which is the third most common cancer in women worldwide. The greatest burden occurs in resource-limited settings, particularly among those who are younger, female, and infected with HIV. Other strains of HPV cause genital warts and other skin warts, and benign tumors of the respiratory tract. These lesions can be especially problematic in individuals whose immune systems are compromised by HIV infection or by drugs given after organ transplantation. Two vaccines, Gardasil and Cervarix, are FDA-approved for the prevention of genital warts and cervical cancer due to HPV.

Science Advance

Repeated Evolutionary Loss of a Papillomavirus Gene. Infection with certain papillomavirus types can lead to the development of carcinomas, particularly in women. NIAID intramural investigators analyzed the sequences of over 300 genetically distinct papillomaviruses, discovering evolutionary gene loss in certain papillomavirus genomes. Understanding the genetic evolution of these viruses helps researchers better understand their function and pathogenesis. (Van Doorslaer & McBride, 2016. PMID 27604338)

Clinical Trials

Evaluating the Effectiveness of the Quadrivalent HPV Vaccine at Preventing Anal HPV Infection in HIV-Infected Men and Women (ACTG A5298). In this study, researchers are evaluating the safety and efficacy of the HPV vaccine Gardasil to prevent anal HPV infection in HIV-infected women. In addition, the study is comparing two different strategies to prevent advanced cervical cancer in women infected with HIV.

HPV Test-and-Treat-Strategy Versus Cytology-based Strategy for Prevention of CIN2+ in HIV-Infected Women (ACTG A5282). This study is comparing two different methods to prevent cervical cancer in women who have HIV. One experimental group will receive cervical cryotherapy (test-and-treat) and another group will a cytology-based management plan involving multiple steps including cytology, colposcopy with directed biopsies, and a surgical procedure as needed. This study will test if these methods are safe and tolerable in women who have HIV.

Bacterial Vaginosis (BV)

BV is the most common infection of the female reproductive tract and occurs when the natural balance between strains of bacteria, or flora, in the vaginal tract is altered. Previous studies have shown that BV increases the risk of sexually transmitted infections, including HIV.

Science Advance

Impact of BV on Levels of Cervical Gamma Delta T Cells May Increase HIV Risk. To better understand how BV can increase the risk of STI, a study explored the relationship between BV and the levels of two types of immune cells found in the female reproductive tract – gamma delta (GD) T cells 1 and 2 – in some of the women enrolled in the Miami WIHS. The researchers found that HIV-uninfected women with abnormal vaginal flora had lower levels of GD1 cells and higher levels of GD2 cells compared with HIV-uninfected women with normal vaginal flora. The lower GD1 cells could indicate a decreased early immune response to infection. Furthermore, higher levels of GD2 cells could increase the number of cells that can be targeted by HIV, since these cells have the CD4 and CCR5 cell-surface receptors necessary for HIV to enter cells and establish infection. (Alcaide et al., 2016 PMID 27078021)

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV)

Viral hepatitis—in particular, HCV infection—is common among persons with HIV/AIDS. As a result of prolonged survival, greater numbers of HIV-infected people are experiencing the long-term complications of HCV and HBV infections, namely cirrhosis, liver failure, and hepatocellular carcinoma (liver cancer). Liver inflammation related to HCV and HBV infection may interfere with the ability to take highly active ART or medications used to treat other HIV-associated conditions.
**Science Advance**

**Exploring Racial/Ethnic Differences in Liver-Related Mortality in HIV/HCV-Coinfected Women.** In the United States, 10–30 percent of HIV-positive individuals are also infected with HCV, and liver-related disease and death from chronic HCV infection remains a significant problem in people coinfected with HIV. Previous studies show that African American women coinfected with HIV and HCV are 60 percent less likely to die from liver-related disease than are coinfected Hispanic or Caucasian women. However, the basis for these disparities is not known. To examine the genetic factors that might explain these racial/ethnic differences, scientists studied participants in the Women’s Interagency HIV Study (WIHS), a multicenter cohort of women at risk for, or currently diagnosed with, HIV. They investigated whether the differences in liver-related mortality were linked with common genetic variants in and around the IFNL3 and IFNL4 genes—two related genes that are associated with HCV and the response to antiviral drugs. The analysis showed that two genetic variants were associated with increased mortality due to HCV. However, these differences did not explain the lower risk of death among African American HIV/HCV-coinfected women, suggesting that other genetic, behavioral, and/or environmental factors may contribute to racial/ethnic differences in liver-related mortality. (Sarkar et al., 2015. PMID 26115445)

**Clinical Trials**

**Viral Hepatitis C Infection Long-Term Cohort Study (V-HICS) (ACTG 5320).** This is a long-term follow-up study for people who have HCV infection alone or who have both HCV and HIV infection. The study will elucidate the impact of successful or unsuccessful HCV treatment on a person’s long term health. It will also help to understand how long resistance to new hepatitis C medications lasts and whether it affects future hepatitis C treatments. The study will analyze each person’s HCV and underlying genetic differences to determine how these influence the success or failure of the HCV treatments, and how treatment affects a person’s quality of life.

**Sofosbuvir-Containing Regimens Without Interferon For Treatment of Acute Hepatitis C Virus (HCV) Infection (SWIFT-C) (ACTG A5327).** People with HCV have a great chance of being cured of the infection when they are treated with a combination of two drugs within the first 6 months of being infected. This study is being conducted to see if a combination of two new drugs, ledipasvir and sofosbuvir, in one pill, can replace pegylated-interferon alfa, a drug given as a weekly injection under the skin, and provide a safer, more effective, and better tolerated treatment for new HCV infection. The fixed-dose combination of ledipasvir and sofosbuvir has been approved by the FDA.

**Tuberculosis (TB)**

Tuberculosis is a major cause of disability and death worldwide. More than 95 percent of TB deaths occur in low- and middle-income countries, according to the World Health Organization. In 2014, 9.6 million people became ill with TB, and 1.5 million people died from the disease. TB is the leading cause of death for people infected with HIV. In 2015, one in three HIV deaths was due to TB. Globally in 2014, an estimated 480,000 people developed multidrug-resistant TB (MDR-TB). TB is a major cause of illness and death in women of reproductive age. Pregnant and postpartum women with latent TB are at higher risk of developing active TB.

**Clinical Trials**

**Pharmacokinetic Interactions of DMPA, Rifampicin and Efavirenz in HIV/TB Co-infected Women (PRIDE-HT) (ACTG A5338).** The purpose of this study is to evaluate the effect of HIV and TB treatment on a commonly used birth control method called depot medroxyprogesterone acetate (DMPA), which is given as an injection every 3 months. The study will establish the best schedule to provide DMPA in women with HIV and TB who are taking efavirenz (EFV; Sustiva; an anti-HIV medication), rifampicin (RIF; an anti-TB medication) and isoniazid (INH; an anti-TB medication) and will ascertain if it is safe to take RIF, EFV and DMPA simultaneously.

**Pharmacokinetics, Tolerability, and Safety of Once-Weekly Rifapentine and Isoniazid in HIV-1-Infected and HIV-1-Uninfected Pregnant and Postpartum Women With Latent Tuberculosis Infection (IMPAACT 2001).** The purpose of this study is to evaluate the treatment of HIV-infected and uninfected pregnant and post-partum women with rifapentine (RPT) and INH for a latent TB infection. This study will enroll HIV-infected and HIV-uninfected pregnant women with latent TB and their infants into two cohorts: Cohort 1 participants will be enrolled in their second trimester of pregnancy, and Cohort 2 participants will be enrolled in their third trimester. All participants will receive 12 directly observed once-weekly doses of RPT, INH, and pyridoxine (vitamin B6).
Fungal Infections

Fungal diseases are often caused by fungi that are common in the environment. Most fungi are not dangerous, but some types can be harmful to health, causing a wide range of issues from mild, rash-like skin diseases to lung infections, meningitis, and bloodstream infections that can be deadly.

Science Advance

Gender Differences in Murine Models of Fungal Infections. Fungal infections frequently occur in people with weakened immune systems who have inhaled fungal spores, but can also occur in healthy individuals. Aspergillosis, which is caused by infection with Aspergillus fumigatus, can result in an allergic reaction that affects the airways and lungs, or it can manifest in a more invasive form that damages organs. Mucormycosis is caused by infection of any member of the fungal group Mucorales. Mucormycosis can be a pulmonary infection, affecting the lungs, sinuses, eyes, and face, or it can be a skin infection when the fungus enters the skin through a cut or wound. Research in an upcoming study (HHSN27220100038I) will examine the effect of sex on fungal infection disease progression and treatment in mice. The major activity to be supported is the evaluation and modification of standardized small animal models of fungal infections caused by Aspergillus fumigatus (TaskA97) or members of the Mucorales (TaskA102), respectively, to determine sex differences, if any, in natural history of disease, immunosuppression, dosing, and response to therapy.

Immunology and Immune-Mediated Diseases

NIAID supports investigations of immunology and immune-mediated diseases and their effects 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 and other immune-mediated diseases.

Immune Response to Vaccinations

NIAID is committed to developing new and improved vaccines. Research to bring about new, more broadly protective vaccines is balanced with efforts to ensure the safety and efficacy of vaccines in various populations. Recent research has shown that immune responses to vaccines can vary between different populations and sexes. Heterogeneous post-vaccination immune responses in men and women have been widely documented for many different vaccines. The underlying causes of these sex differences are an area of active investigation.

Science Advance

Sex Difference in Immune Response to Smallpox Vaccination. IMVAMUNE is a smallpox vaccine based on the modified vaccinia Ankara (MVA) virus. It was developed as a way to prepare for the possibility of a bioterrorist attack using smallpox. Recently, it has been shown that immune responses to vaccines can vary among different populations. To test whether there are sex-based differences in the immune response to IMVAMUNE, researchers compared responses from 275 individuals (136 men, 139 women) in a meta-analysis of data from three randomized trials of IMVAMUNE. In comparing healthy men and women who had not been previously exposed to smallpox vaccine, the results demonstrated that men showed higher levels of antibody against smallpox. These findings suggest that sex-based differences in immune response could affect the efficacy of IMVAMUNE and other MVA-based vaccines. (Troy, Hill, Ewell, & Frey, 2015. PMID 26319063)

Immune Changes in Pregnancy

Pregnancy alters immune function. It has been suggested that pregnancy causes an immunosuppressive state that prevents the mother’s immune system from attacking the fetus and results in an increased susceptibility to infection. During pregnancy, the placenta performs many critical functions, including protecting the fetus from infection. Researchers are trying to develop new technologies to understand how the placenta functions and how to better protect the fetus against infection.

Clinical Trial

Pregnancy Immune Function. Progress in treating and managing infections during pregnancy will require further understanding of the changes to the immune system that occur during pregnancy. NIAID intramural scientists recently completed a clinical trial that evaluated blood samples drawn from pregnant women during early, mid, and
late pregnancy and postpartum for changes in the innate immune system and compared them to those of healthy, non-pregnant women. Changes in the cytokine profile and in the lymphocyte and natural killer cell populations are being identified. ([NCT01200979](https://clinicaltrials.gov/show/NCT01200979))

**Science Advance**

A Novel 3D Culture System to Study the Development and Microbial Resistance of the Human Placenta. The human placenta is covered with a protective layer of multinucleated cells (cells with many nuclei) that serves as a barrier to prevent the transfer of toxins, bacteria, and viruses from mother to fetus. The molecular mechanisms that control the formation these specialized cells, called syncytiotrophoblasts are not well understood. To study these mechanisms, scientists devised a three-dimensional (3D) system for culturing (growing) cells that models placental development and function. This 3D cell culture model could provide a means to study the process by which trophoblasts fuse together to become syncytiotrophoblasts and develop resistance to microbial infection that protects the developing fetus. In addition, this culture system may be very useful in elucidating how some viruses, such as Zika virus, are able to penetrate the placental barrier and cause harm to the developing fetus. ([McConkey et al., 2016. PMID26973875](https://www.ncbi.nlm.nih.gov/pubmed/26973875))

**Asthma**

Asthma is a severe and chronic disease that causes wheezing, breathlessness, chest tightness, and coughing. It affects more than 230 million people worldwide, including more than 18 million adults and 7 million children in the United States. The prevalence of asthma in girls increases after puberty. Early prevention of asthma is essential to reducing the burden of this high-impact disease in adolescent girls.

**Urban Environment and Childhood Asthma (URECA)**

Asthma severity increases in girls during and after puberty, whereas it tends to improve in boys. Subjects in the URECA birth cohort, funded by NIAID, are reaching puberty. NIAID plans to support research to understand the immunologic mechanisms through which this sex-based difference occurs in association with pubertal changes. This plan will be in place by the middle of 2017.

**Role of Epigenetics in Sex-Specific Changes in Asthma Severity and Incidence.** The effect of puberty on asthma may have its basis in epigenetic modifications, or changes in gene expression caused by environmental factors such as hormones, rather than in alteration of the genetic code itself. Some studies have suggested that sex hormones lead to modifications of the gene GATA3, which regulates the immune response associated with asthma. In FY 2016, NIAID awarded a new research grant ([1R01 AI121226-01](https://www.grants.nih.gov/grants/guide/pa-files/PA-16-010.html)) to study the gender switch in adolescent asthma. In this project, researchers are examining asthma and associated risk factors during adolescence at the genome level, and collecting epigenomic, genomic, and transcriptomic data from two well-characterized groups of individuals that researchers have followed since birth. The overall goal is to record the extent of genome-wide DNA methylation—a type of epigenetic modification—and its change in adolescence, and to identify sex-specific effects in association with changes in asthma severity and incidence. Findings from this project could potentially lower incidence and promote remission of asthma during adolescence.

**Allergy**

Allergic diseases are very prevalent in the United States and around the world. The development, history, genetics, diagnosis, management, and prevention of these conditions are important scientific research areas for NIAID. Severe allergic reactions and anaphylaxis, a rapid onset, potentially life-threatening allergic reaction, are more common in adult women than in adult men, although the mechanism underlying this disparity is not well understood.

**Science Advance**

Estrogen Worsens Allergic Reactions in Mice. To study sex differences in severe allergic reactions, NIAID intramural researchers used a mouse model of anaphylaxis. They used two methods to investigate estrogen involvement in severe allergic reactions: pretreatment of the mice with a drug to block estrogen activity or surgical removal of the ovaries. Both of these methods eliminated the enhanced severity of anaphylactic responses in female animals. Severity was restored following administration of estradiol (a form of estrogen) in mice that had their ovaries removed. The study further showed that estradiol increased tissue expression of endothelial nitric oxide synthase (eNOS), the enzyme responsible for producing nitric oxide (NO). Nitric oxide is known to regulate many
processes involved in anaphylactic shock, such as vasodilation and vascular leakage. Blockage of NOS activity with an inhibitor, or genetic eNOS deficiency, abolished the sex-related differences. This study establishes estrogen’s contribution to anaphylaxis severity and delineates the mechanisms of its action through regulation of eNOS expression and nitric oxide production. (Hox et al., 2015. PMID 25553642)

Autoimmune Diseases

Autoimmune diseases are a group of more than 80 chronic, and often disabling, illnesses that develop when underlying defects in the immune system lead the body to attack its own (“self”) organs, tissues, and cells. Some of the more common autoimmune diseases include rheumatoid arthritis, type 1 diabetes, multiple sclerosis, celiac disease, systemic lupus erythematosus, and inflammatory bowel disease. Many autoimmune diseases disproportionately affect women, and this group of diseases is among the leading causes of death for young and middle-aged women. NIAID supports research and promotes progress toward conquering autoimmune diseases through a wide range of research projects and programs.

Systemic Lupus Erythematosus (SLE)

SLE, more commonly known as lupus, is a relapsing autoimmune disease that causes inflammation that can affect many body systems, including the central nervous system, joints, skin, kidneys, blood cells, heart, and lungs. Approximately 322,000 Americans are diagnosed with, or suspected of having, SLE. Ninety percent of people with lupus are women, and the age of onset generally is between 15 and 45 years. Lupus is more common in black, Hispanic, Native American, and Asian women than in white women.

Science Advance

New Insights into Disease Flares in Systemic Lupus Erythematosus (SLE). People with SLE have high serum levels of autoantibodies—antibodies that react against the body’s own cells and tissues. These autoantibodies are continuously present in SLE, but the levels of some autoantibodies, and of antibody-secreting immune cells, called B cells, increase in patients suffering a relapse, or “flare,” of the disease. NIAID-supported researchers used state-of-the-art techniques to create a detailed picture of the interrelationships, diversity, and origins of autoantibody-producing cells from people with SLE during disease flares. They then compared them to the conventional antibody response that occurs in healthy people after immunization (vaccination). Their analysis indicates that autoantibody-producing B cells in people with SLE arise via several distinct pathways, including pathways that differ from those of a conventional immune response. And, unlike antibody-producing cells that form in response to vaccines, a substantial number of these autoreactive cells persist in the circulation of people with SLE for several months. These findings shed light on the disease process in SLE, help explain the benefit of existing therapies that target B cells, and could facilitate the design of new therapies. (Tipton et al., 2015. PMID 26006014)

Ten Genes Newly Associated with the Heritability of Lupus Among Asians. SLE is approximately ten times more common in women than in men. In addition, Asians have a higher SLE incidence, more severe disease, and greater risk of organ damage than people of European ancestry. Although SLE is known to have a strong genetic component, only about 10 percent of disease heritability is explained by previously identified genetic variations. To identify genetic variants associated with SLE in individuals of Asian ancestry, NIAID-funded researchers studied the DNA of thousands of individuals, either with SLE or unaffected, from six East Asian populations, focusing on immune-related regions, or loci, of the genome. By combining their data with those of previous studies to narrow these regions, they identified ten genes newly associated with a predisposition for SLE, and confirmed twenty genetic regions previously suspected to be associated with SLE. Six of the ten newly identified genes are also associated with other autoimmune diseases. Together with previous studies, these results increase the explained heritability of SLE to 24 percent among individuals of Asian descent. These findings provide valuable insight into the pathogenesis and manifestations of lupus and point to new targets for treatment of SLE. (Sun et al., 2016. PMID 26808113)

Systems-Level Analysis Identifies a Potential Biochemical Signature of Lupus. Toll-like receptors (TLR) are cell-surface proteins involved in the initial recognition of microbes, and activation of TLRs leads to an inflammatory immune response. When TLRs inappropriately recognize “self” molecules, the inflammatory immune response can lead to autoimmune diseases such as SLE, or lupus. To investigate how the response to TLR activation can vary across cells of the immune system, NIAID-supported scientists initially analyzed blood samples from healthy volunteers. Using different types of stimuli, the researchers activated the TLR proteins and measured changes in the
expression patterns of different immune signaling proteins and factors called cytokines that affect immune function. Systems-wide analyses revealed that in newly diagnosed SLE volunteers, white blood cells called monocytes produced increased levels of particular cytokines compared with monocytes from healthy donors, defining a potential biochemical signature for SLE. These findings provide a systems-level framework that can be applied to study immune perturbations in people with inflammatory diseases such as SLE and might be used to help diagnose and treat these diseases. (O’Gorman et al., 2015. PMID 26037552)

Cell Type Identified as Key Player in Lupus Initiation and Aggravation. NIAID intramural researchers recently proved that a rare type of immune cell, with immature phenotype and quick turnover in healthy individuals, plays a key role in lupus initiation and aggravation. These atypical natural killer (NK) cells were shown to be expanded in number during chronic innate immune stimulation, such as in lupus and other conditions that involve chronic inflammation. The researchers’ work also suggests that NK cell types can affect the priming and progression of diseases like lupus. This type of mechanistic information on pathways and cell populations provides valuable insights on how lupus progresses, might be used as a specific biomarker of disease, and, ultimately, identifies points in the disease process that could be disrupted through targeted therapies. (Voynova, Qi, Scott, & Bolland, 2015. PMID 26109646)

Personalized Immunomonitoring Uncovers Molecular Networks that Stratify SLE Patients. Scientists have previously identified several sets of genes, termed modules or signatures, which can be dysregulated in a coordinated manner in individuals with SLE. The first and most widely investigated of these is the interferon response signature. Researchers compared these modules among 158 pediatric participants with SLE over a 4-year period and found seven distinct genetic patterns, one correlating with disease progression to kidney inflammation (nephritis). These genetic patterns will help physicians diagnose SLE more accurately and prescribe more effective therapy for the individual patient. (Banchereau et al., 2016. PMID 27040498)

Multiple Sclerosis (MS)

MS, an inflammatory disease of the central nervous system, is the leading cause of neurologic disability among young adults, causing visual disturbances, muscle weakness, and loss of coordination. Severe, progressive cases can result in partial or complete paralysis. MS affects about 400,000 Americans, and women are affected about twice as frequently than men.

Science Advance

Functional Differences in Immune Cells Provide Clues to Disease Process in Multiple Sclerosis. MS is thought to result from immune cells called autoreactive (self-reactive) T cells that target myelin, the sheath that surrounds and insulates nerve fibers. Since individuals with MS have similar numbers of myelin-reactive T cells as healthy people, researchers looked for possible functional differences between the myelin-reactive T cells. They compared the production of cytokines (small proteins that regulate the immune system) by these cells and found that the T cells from people with MS produced more inflammation-causing cytokines such as IL-17 compared with T cells from healthy people, whereas T cells from healthy people produced more of an anti-inflammatory cytokine called IL-10. The researchers also identified some striking differences between the genetic profiles of myelin-reactive T cells in people with MS and healthy individuals. These findings suggest that functional differences between myelin-specific T cells from people with MS and healthy individuals play a role in disease development. (Cao et al., 2015. PMID 25972006)

Clinical Trial

Stem Cell Transplants May Halt Progression of Multiple Sclerosis. A treatment that may be promising for achieving long-term remission of MS involves resetting the immune system through a combination of high-dose chemotherapy and hematopoietic stem-cell transplantation (HSCT). To test this approach in MS patients with active relapsing-remitting disease unresponsive to conventional treatment, researchers designed a clinical trial called High Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS). The HALT-MS study enrolled 25 participants experiencing active relapsing-remitting MS with worsening neurological disability, despite taking standard medications. Researchers harvested stem cells from the patient’s own bone marrow. Participants next received high-dose chemotherapy to destroy their immune cells, and then received their previously harvested stem cells to reset and then rebuild their immune systems. After 3 years, 78 percent of participants remained in remission. The HALT-MS study researchers plan to follow participants for a total of 5 years. Final
results from this and similar studies will help inform the design of larger clinical trials to further evaluate this
treatment approach for people with MS. (Nash et al., 2015. PMID 25546364)

**Rheumatoid Arthritis (RA)**

Rheumatoid arthritis is an autoimmune inflammatory disease that causes pain, swelling, and stiffness in the joints
and can result in serious joint damage. About 1.5 million Americans have RA, and two to three times as many
women as men are affected.

**Science Advance**

**Rheumatoid Arthritis–Associated Antibodies May Arise from Mucosal Immune Responses.** Rheumatoid
arthritis (RA) is associated with the production of autoantibodies—antibodies that can bind to and attack normal
tissues within the body and appear to play a major role in disease development. Determining the source of these
autoantibodies is thus key to better understanding of how RA develops. Scientists isolated antibody-producing cells
called plasmablasts from individuals known to be at risk of developing RA and compared them to plasmablasts from
subjects with established RA and from healthy controls not at risk for RA. Individuals at risk for RA exhibited a
higher frequency of plasmablasts producing antibodies of the IgA type, which is associated with immune responses
from mucosal membranes—thin layers of tissue that line body cavities and surround internal organs. Those at risk
for RA also showed increased serum levels of disease-associated IgA autoantibodies. These results suggest that
some autoantibodies that drive the development of RA may arise from immune responses at mucosal surfaces, and
may also provide a means of identifying individuals at the greatest risk of progressing from at-risk status to clinical
disease. (Kinslow et al., 2016. PMID 27273876)

**The Microbiome and Autoimmunity**

Microbes inhabit just about every part of the human body. Sometimes they cause sickness, but most of the time
microorganisms live in harmony with their human hosts, providing vital functions essential for human survival.
NIAID participates in the NIH Human Microbiome Project, which is mapping the microbial make-up, or
microbiome, of humans to better understand the role of microbes in health and disease. Some NIAID projects study
how the microbiome influences immune responses.

**Science Advance**

**Gut Microbiota Promote Autoimmune Arthritis by Triggering Migration of Gut T Cells to Systemic Sites.** Gut microbiota are known to influence the development and function of the immune system and to play a role in
immune mediated diseases such as autoimmunity. The question remains of how microbiota colonizing the gut can
influence development of disease at sites distant from the gut. Researchers addressed this question using a mouse
model of autoimmune arthritis that was shown to be dependent on a type of bacteria present in the gut microbiota,
segmented filamentous bacteria (SFB). Their results demonstrate that SFB in the gut trigger expansion of immune
cells called follicular helper T cells in the gut, and induce migration of these cells from the gut to the lymphatic
system, where antibody production occurs. This expansion and migration of follicular helper T cells led to increased
autoantibody production and disease exacerbation. (Teng et al., 2016. PMID 27096318)

**Systemic Sclerosis (Scleroderma)**

Scleroderma is a group of autoimmune diseases in which the immune system is thought to stimulate cells called
fibroblasts, which then produce too much of the fibrous protein collagen. Systemic sclerosis is the form of the
disease that not only includes the skin but also involves the tissues beneath the skin, 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—especially middle-aged
women and African American women—are affected more than men.

**Clinical Trial**

**The Scleroderma Cyclophosphamide or Transplantation (SCOT) study is comparing the safety and potential
usefulness for scleroderma of high doses of drugs to suppress the immune system followed by transplantation of
immune system stem cells versus monthly high doses of the immunosuppressive drug cyclophosphamide. The
hypothesis is that high-dose immunosuppressive therapy will destroy the malfunctioning immune system, and
replacement with immature immune cells will permit the development of a healthy immune system, inducing a long-term remission or even eradicating the disease. High doses of cyclophosphamide may reduce symptoms more effectively than the standard low-dose therapy. The follow-up phase of the study is complete and the data are being analyzed. More information is available at [http://www.sclerodermatrial.org/](http://www.sclerodermatrial.org/) (NCT00114530).

### NIH Strategic Plan for Women’s Health Research

The **Trans-NIAID Women's Health Research Work Group** focuses on women's health and gender-based research activities that advance the mission and research priorities of NIAID and provides recommendations for future women's health research opportunities. The work group performs the following functions:

- Heavens awareness across NIAID of the importance and substance of women’s health and gender-based research
- Develops a common framework for identifying and assessing gender-based and women’s health research
- Encourages trans-NIAID and trans-NIH collaborations on women’s health and gender-based research activities
- Coordinates various NIAID-wide presentations on topics such as the effects of antibiotics on the vaginal microbiome and health, and sex as a biological variable.

### Inclusion

NIAID supports many research studies that focus on better understanding of gender differences in disease outcomes, as reflected in the Accomplishments and Activities section above.

Over the last two decades, researchers and clinicians have acknowledged that there are critical scientific gaps in the evidence base for clinical care of pregnant women. The PHASES project, funded by NIAID, seeks to increase enrollment of pregnant women in ethically appropriate clinical research through development of a carefully vetted ethical framework and guidance document for researchers, Institutional Review Boards, and regulators. The focus of the effort is research on (a) HIV prevention methods and (b) novel HIV treatment regimens, including treatment for women with co-morbidities such as HIV/TB coinfection. This large multi-institution project, initiated in 2014, includes a project team of bioethics experts, legal and regulatory scholars, clinical researchers, and community stakeholders who will address the challenges and barriers of inclusion of pregnant women in research (Krubiner et al., 2016. PMID 27490637). More information is available at [http://bioethics.unc.edu/phases/](http://bioethics.unc.edu/phases/).

Finally, NIAID structured several longitudinal HIV/AIDS studies and programs, described above, to enable the study of sex and gender differences, including the following:

- The WIHS is closely linked to the MACS, a study of MSM, to ensure that data collected in the two studies can be combined and compared whenever appropriate. Studies that compare outcomes for men and women in pharmacology, cardiovascular disease, aging, sleep patterns, metabolic disorders, mental health, and neurologic diseases are ongoing. These projects have demonstrated differences in the pharmacology of antiretroviral drugs and differences in the clinical outcomes between men and women with HIV in the United States.
- The International Epidemiology Databases to Evaluate AIDS (IeDEA) program combines data from nearly 1 million people with HIV globally. With these data, researchers can evaluate gender differences in disease outcomes and therapy response.

### STEM Career Development Efforts

NIAID continues to cosponsor the Building Interdisciplinary Research Careers in Women’s Health mentored career development awards, which support the development of women’s health researchers. This activity supports NIH ORWH strategic goal 6.2, **Lead the way in encouraging institutions to recognize mentoring as an essential component of building career success in their training programs.** NIAID also continues to cosponsor the Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers, which aims to encourage individuals to re-enter an active research career after after an interruption for family responsibilities.
The Inter-CFAR Collaboration on HIV Research in Women develops new strategies for future research to address HIV-related issues unique to women and promotes career development among junior investigators in this field.

NIAID actively supports NIH efforts to increase diversity in the scientific workforce by contributing to internal working groups, publicizing ongoing opportunities, and participating in NIH-wide efforts such as the Building Infrastructure Leading to Diversity initiative.

NIAID’s outreach program to populations underrepresented in biomedical research, the Intramural NIAID Research Opportunities (INRO) program, has been successful in recruiting women (undergraduate seniors and graduate students) to its annual 4-day program. Of the 202 applications submitted for INRO between 2015 and 2016, 133 were female. Of the 44 selected students, 24 were female. In addition, in 2015 and 2016, NIAID accepted three young women (high school students) from the Bnos Yisroel Scientific Bridge Program in NIAID’s Summer Intern Program, for lab work, mentoring, and attending guest lectures.

Research Initiatives

NIAID supports a number of initiatives on research related to women’s health, including the following:

**Increased Knowledge and Innovative Strategies to Reduce HIV Incidence-iKnow Projects.** The purpose of this FOA is to devise optimal strategies to improve the identification of persons unaware of their HIV infection and successfully link them to HIV testing, treatment, and prevention interventions; and to develop and examine the feasibility and acceptability of novel integrated interventions of biomedical and behavioral strategies that substantially reduce the likelihood of onward HIV transmission in these populations. [PAR-16-117](#)

**Methods for Prevention Packages Program IV (MP3 IV)** The purpose of this FOA is to promote multidisciplinary research programs that (1) devise optimal HIV prevention packages (combination interventions) for specific populations and (2) perform feasibility and acceptability studies to demonstrate that the proposed prevention package is acceptable to the target population and the study design is appropriate and feasible. This FOA is intended to encourage collaborations between behavioral and biomedical clinical specialists, epidemiologists, mathematical modelers, and clinical research specialists. [PAR-16-124](#)

**Harnessing Big Data to Halt HIV** The purpose of this FOA is to promote innovative research using Big Data Science (BDS) to understand the complex and substantially interrelated factors that place persons at risk of HIV infection and that influence their HIV treatment course. BDS approaches have the potential to bring together data on populations such that the epidemiology of risk and care can take into account the complexity of contextual factors in individual’s lives. [PA-15-273](#)

**Administrative Supplements for Research on Sex/Gender Differences.** This FOA was reissued in 2015 and 2016 to provide administrative supplements to support research highlighting the impact of sex/gender in human health and illness. The research will address at least one of following objectives: increasing sex differences research in basic science studies; incorporating findings of sex/gender in the design and development of new technologies, medical devices, or therapeutic drugs; or actualizing personalized prevention, diagnostics, and therapeutics for girls and women (PA-16-066 and PA-15-034).

**Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations.** This FOA was issued in FY 2016 to provide administrative supplements to support research focused on health issues affecting SGM populations, such as lesbian, gay, bisexual, and transgender people, and individuals with differences or disorders of sexual development (sometimes referred to as “intersex” or as specific diagnoses). The research will address areas beyond HIV/AIDS, including, but not limited to: studies on increased disease risk; behavioral and social health; approaches to personalized medicine; access to care; reproductive and sexual development; and resilience (PA-15-329).

Conferences and Publications

The **Inter-CFAR Joint Symposium on HIV Research in Women** was held December 8-9, 2014, to (1) identify gaps in knowledge in research related to HIV and women and develop strategies that will move the field forward, (2) generate collaborative activity between the different CFARs and with other research networks highlighting cutting-edge science, and (3) promote and emphasize opportunities for young investigators. The most recent meeting was hosted by the University of Washington CFAR on November 4-6, 2015. The focus was (1) HIV research in
women and children, (2) HIV malignancies, (3) progress in HIV/AIDS combination prevention research and implementation, and (4) cohort research on HIV and co-morbidities.

Guest editors and authors from NIH and the Bill & Melinda Gates Foundation facilitated the publication of a special issue of the journal Vaccine (Volume 33, Issue 47) in 2015, titled Advancing Maternal Immunization Programs through Research in Low and Medium Income Countries. Articles addressed current and future prospects through specific examples and literature reviews. The article Maternal immunization efforts of National Institutes of Health described NIAID-sponsored studies of licensed vaccines during pregnancy. (Rubin et al., 2015. PMID 26458798)

NIH collaborated with the International Alliance for Biological Standardization to organize the Harmonized Safety Monitoring of Immunization in Pregnancy International Consensus Conference in Bethesda, MD, on March 29–30, 2016. Experts highlighted a need for harmonized study protocols, case definitions, and a globally concerted effort to move toward enhanced surveillance. The report from this conference will be published in the journal Biologicals.

Staff from NIAID, NICHD, and NCI are participants in Global Alignment of Immunization Safety Assessment in Pregnancy, a 2-year global project coordinated by the Brighton Collaboration Foundation. The project’s objective is to develop standards, guidance, and tools toward harmonized assessments of maternal, fetal, and neonatal health outcomes. Multiple working groups are preparing manuscripts to be published in 2017.

The Assistant Secretary for Health charged the National Vaccine Advisory Committee (NVAC) with reviewing the state of maternal immunizations and proposing recommendations. NVAC established the Maternal Immunization Working Group (MIWG) in August 2012. NIAID representatives served as members of the MIWG and attended conferences during the following 4 years. The MIWG identified four main areas of discussion: 1) ethical issues, 2) policy issues, 3) preclinical and clinical research issues, and 4) provider education and support issues. In 2013 and in 2016, MIWG provided NVAC with documents that addressed these areas.

**Health Disparities**

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

- WIHS
- IeDEA
- ASPIRE, and several MTN studies
- ADAPT and other PreP studies
- HIV Infection Has a Small but Negative Effect on Cognitive Function in Women.
- Untreated HIV Infection Has No Association with Low Bone Mineral Density
- PROMISE Study, and other studies to evaluate approaches for PMTCT
- Host and Parasite Factors That Influence Susceptibility to Malaria Infection and Disease During Pregnancy and Early Childhood in Mali
- Zika in Infancy and Pregnancy (ZIP)
- Exploring Racial/Ethnic Differences in Liver-Related Mortality in HIV/HCV-Coinfected Women
- Viral Hepatitis C Infection Long-Term Cohort Study (V-HICS)
- Ten Genes Newly Associated with the Heritability of Lupus Among Asians
References


Zhang, H., & Holloway, J.W. (2016). Does epigenetic methylation explain the gender-switch in adolescent asthma? (Grant No. R01AI121226), National Institute of Allergy and Infectious Diseases grant, University of Memphis, Memphis, TN.