

# NIAID Women’s Health and Sex/Gender Influences Research (FY 2017-2018)

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## 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 clinical studies on treatment and prevention of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), autoimmune diseases, 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. Accomplishments in HIV/AIDS include development and testing of intravaginal rings containing antiretroviral drugs, vaccine research that evaluates the safety and efficacy of a broadly neutralizing monoclonal antibody in reducing incidence of HIV/AIDS infection in African women, and therapeutic research studies analyzing possible adverse pregnancy outcomes of antiretroviral therapy (ART). Also noted is a clinical trial demonstrating the effectiveness of an ART regimen to minimize the risk of mother-to-child transmission of HIV for the duration of breastfeeding. Other highlights include an investigation into a potential therapy for Zika virus infection and studies examining hormonal influences on influenza infection. We report on basic research that could lead to an improved understanding of the inflammation response that occurs in autoimmune diseases that disproportionately affect women, such as systemic lupus erythematosus (SLE); and insights into immunological changes during 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 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.

## Accomplishments and Activities

### HIV/AIDS

#### **Working Toward a Safe, Effective, and Acceptable Microbicide for HIV**

Women face a greater risk of acquiring HIV than men in part because of substantial exposure to semen at mucosal membrane sites, prevalence of nonconsensual sex, and sex without condom use. Compounding these risks for women are the unknown risk behaviors of their male sexual partners, such as injection drug use or having sex with men. The Microbicide Trials Network (MTN) (<http://www.mtnstopshiv.org/>) was formed by NIAID and NIH partners in 2006 as a worldwide collaborative clinical trials network 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 US 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. 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. MTN is enrolling and/or conducting several studies evaluating the safety and adherence to use of a vaginal ring containing the antiretroviral drug dapivirine, including the following:

- [MTN-044/IPM 053/CCN019](#): A Phase I study to assess the pharmacokinetics and safety of a vaginal ring containing dapivirine and levonorgestrel used for 90 days. The study will also investigate the acceptability of and adherence to this HIV prevention-plus-contraception method.
- [MTN 034](#) (REACH study): In 2019, NIAID will begin enrolling participants in a Phase IIa study to assess the safety of and adherence to the dapivirine vaginal ring and oral pre-exposure prophylaxis (PrEP) in adolescent girls and young women in sub-Saharan Africa. PrEP is a strategy in which healthy people routinely take one or

more antiretroviral drugs to reduce their risk of getting HIV. The trial will collect safety and adherence data over the course of study product use to more fully understand issues that affect product uptake.

- [MTN 029, MTN-029/IPM 039](#): A Phase I study designed to assess the presence of dapivirine in breast milk when the drug is delivered via vaginal ring. The primary objective of this trial is to assess the pharmacokinetics as well as safety, tolerability, and adherence to the ring, when used for 14 consecutive days by lactating women.

### **Evaluating the Efficacy of Long-Acting HIV Pre-Exposure Prophylaxis (PrEP)**

The NIAID HIV Prevention Trials Network (HPTN) was established in 2000 as a worldwide collaborative clinical trials network to develop and test the safety and efficacy of primarily non-vaccine prevention strategies such as PrEP. The one currently validated PrEP method involves taking a daily dose of two antiretrovirals, tenofovir and emtricitabine, in a single pill marketed as Truvada. NIAID supports research to develop longer-acting forms of HIV prevention. In 2017, the HPTN announced the initiation of the first large-scale study in women of a long-acting injectable drug to prevent HIV, called cabotegravir (CAB). The study, [HPTN 084](#) is a Phase III study comparing the long-acting injectable CAB to a combination of daily oral PrEP in 3,200 HIV-uninfected, sexually active women in sub-Saharan Africa. The HPTN is also currently conducting a Phase III study, [HPTN 083](#), to evaluate CAB versus daily oral PrEP in populations of men who have sex with men and transgender women who have sex with men. If found to be safe and effective for HIV PrEP, injectable CAB may be an easier, more desirable, and discreet alternative to daily oral PrEP for some women. More information is available at <http://www.hptn.org/>.

### **Risk Factors Identified for Cytomegalovirus Infection of Infants Born to HIV-Infected Women**

Cytomegalovirus (CMV)—a common virus that infects people of all ages—is a cause of infection at birth, which may lead to developmental delays and hearing loss. People infected with CMV can shed the virus through bodily fluids such as urine, saliva, or breast milk, but little is known about the relevance of CMV shedding in the context of persons infected with HIV. As part of the NIAID-funded HPTN network, investigators examined whether pregnant, HIV-positive women shed CMV in their urine and whether that could increase the chances of transmitting CMV to their infant. The researchers evaluated a subset of the mother-infant pairs in the perinatal [HPTN 040](#) study, which enrolled women who were identified as HIV-infected around the time they gave birth, and who therefore had not received ART before labor. Researchers found that maternal CMV urinary shedding at the time of birth is a significant risk factor for both CMV and HIV transmission to infants born to women who did not receive ART during pregnancy (Adachi K et al, 2017. [PMID 8369278](#))

### **Continuing Anti-HIV Therapy After Pregnancy in Non-Breastfeeding Women Provides Benefits**

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), sponsored by NIAID and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), 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://impaactnetwork.org/>.

As part of the NIAID-funded, Promoting Maternal and Infant Survival Everywhere (PROMISE) study, researchers found that maternal and infant ART strategies were equally safe and effective at preventing transmission of HIV to the infant for up to 24 months of breastfeeding. These results show that while the preferred strategy of treating the mother as part of lifelong ART is highly effective at reducing mother-to-child HIV transmission, infant ART is an effective and safe alternative (Flynn et al 2018. [PMID 29239901](#)). To further our understanding of the benefits of continuing anti-HIV therapy for postpartum women, another component of the PROMISE study (the “HAART Standard”) was designed to assess the risks and benefits of continued ART compared with stopping ART after delivery and restarting when clinically indicated by a drop in CD4 T-cell counts below a certain level, or by other factors. Findings from this study provided further evidence that ART benefits women with early-stage HIV infection (Currier JS et al., 2017. [PMID 28489856](#)).

### **Composition of Female Genital Tract Microbiome May Affect Risk of HIV Infection**

HIV prevalence in young African women is up to eight-fold higher than in young African men, suggesting that biological factors in the female genital tract may increase susceptibility to infection. Scientists previously hypothesized that certain types of bacteria that naturally colonize the female genital tract may be linked to decreased rates of HIV infection. To test this hypothesis, NIAID-funded researchers turned to Females Rising through

Education, Support and Health (FRESH), an ongoing trial funded by the Bill & Melinda Gates Foundation, that comprises healthy, HIV-uninfected, 18- to 23-year-old black South African women who are provided with intensive HIV prevention counseling and HIV testing. Researchers found that distinct bacterial types and communities are associated with an increased risk of HIV infection. The results suggest that South African women may be at increased risk of HIV infection based on their reproductive tract microbiota and emphasize the importance of considering the microbiome when developing new approaches to reduce HIV infection (Gosmann C et al., 2017. [PMID 28087240](#)).

### **Evaluating Promising HIV Vaccine Candidates**

The HIV Vaccine Trials Network (HVTN) is an international collaboration of scientists searching for an effective and safe HIV vaccine. The purpose of the HVTN 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 regarding safety, tolerability, and immune responses. More information is available at <http://www.hvtn.org/>.

Two ongoing HVTN studies are evaluating the safety and efficacy of promising HIV vaccine candidates:

- [HVTN 705](#), (Imbokodo study): A large Phase IIb proof-of-concept study evaluating the safety, tolerability, and efficacy of a prime/boost vaccine regimen among women in sub-Saharan Africa. The study will enroll an estimated 2,600 participants and will evaluate two vaccines, called Ad26.Mos4.HIV (Ad26 vaccine) and Clade C gp140 (protein vaccine).
- [HVTN 703/HPTN 081](#): A Phase IIb study to evaluate the safety and efficacy of VRC01, a broadly neutralizing monoclonal antibody developed by NIAID, in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa. Full enrollment was reached in September 2018, and 1,885 participants are now in follow-up study.

### **Characterizing Health Disparities Among Women Living with HIV**

The Women's Interagency HIV Study (WIHS) (<https://statepi.jhsph.edu/wihs/wordpress/>) is the largest observational study of HIV-infected women and includes participants living in 10 US metropolitan areas. WIHS has an active research program investigating health disparities among HIV-positive women, particularly in the Southern United States. WIHS investigators published a study showing that the prevalence of sexually transmitted infections was inversely correlated with voter turnout and positively associated with felony voter disenfranchisement (Haley et al., 2018. [PMID 30442564](#)). An analysis of WIHS data showed a significant association between sustained perceived social support and increased ART adherence in the WIHS (Chandran et al., 2018. [PMID 30311104](#)). WIHS data also demonstrated that food insecurity is associated with elevated levels of inflammation among HIV-positive women regardless of HIV control (Leddy et al., 2018. [PMID 30165648](#)), and unstable housing reduces the likelihood of viral suppression by 51% and the probability of having adequate white blood cell count by 53% (Galárraga et al., 2018. [PMID 30153546](#)).

### **Chronic Hepatitis C Infection in Women May Affect Response to Anti-HIV Therapy**

In the United States, one in four people living with HIV are also infected with hepatitis C virus (HCV). Suppressing HIV levels through ART improves long-term health and reduces transmission of HIV to uninfected sexual partners. Yet the effects of chronic HCV co-infection on the effectiveness of ART for HIV infection are unclear, especially among women. To estimate the effects of chronic HCV on the ability of ART to control HIV in women for up to 15 years, researchers analyzed WIHS data and found that chronic HCV infection may negatively affect early HIV viral response to ART, highlighting the need to carefully monitor HIV care and facilitate access to HCV treatment among people with HIV/HCV co-infection (Willis SJ et al., 2018. [PMID 29334550](#)).

### **Sex-Based Differences in ART Initiation, Switching, and Treatment Interruptions**

The International Epidemiology Databases to Evaluate AIDS (IeDEA) was established by NIAID in 2006 to bring together HIV 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 7,800 women living in the United States or Canada. More information is available at <http://www.iedea.org/>.

In 2018, researchers published a collaborative analysis of IeDEA cohort data evaluating sex-based differences in HIV treatment patterns among more than 700,000 participants in six regions across the Americas, Asia, and Africa. Results from the study suggest that women from North America and southern Africa regions were significantly more likely than men to switch their first-line regimen, and that only in North America were women more likely to have treatment interruptions than men. Future studies to define possible reasons for switching (toxicity, pregnancy, drug interactions or resistance) are essential to understanding the sex differences observed in treatment changes and interruption (Giles ML et al., 2018. [PMID 29956882](#)).

### **Correlation Between ART Program Attrition and Pregnancy in East Africa**

Investigators used data from the IeDEA-East Africa collaboration to examine the impact of pregnancy on treatment and found that pregnant women constituted an increasing proportion of individuals initiating ART (5.3% in 2004, 12.2% in 2014) (Holmes CB, et al., 2018. [PMID 29342180](#)). Pregnant women were at higher risk of loss-to-follow-up (LTFU) care than males; however, older adolescents had higher rates of LTFU compared with adults or younger adolescents, primarily driven by both pregnant and non-pregnant females. These data can help programs identify those at greatest risk for LTFU and address efforts to support and retain this population (Nuwaaba-Biribonwoha, et al., 2018. [PMID 30225908](#)).

### **Adverse Pregnancy Outcomes of Antiretroviral Therapy**

The Centers for AIDS Research (CFAR) is a unique trans-NIH program that provides infrastructure to support interdisciplinary, peer-reviewed HIV/AIDS research. There are currently 19 CFARs at academic and research institutions throughout the United States. In 2017–2018, CFARs supported more than 30 women's health pilot projects through the CFAR Developmental Cores. More information is available at <https://www.niaid.nih.gov/research/centers-aids-research>.

Women with HIV are at risk of infecting their children during pregnancy, during birth, or shortly thereafter. NIAID-funded researchers analyzed data on pregnant HIV-infected women collected from two US-based studies. The women received one of three common three-drug ART regimens. Overall, women in the three groups had similar risks of having infants born prematurely or with low birthweight. An analysis of the women who started treatment before conception suggested that those treated with tenofovir, emtricitabine, and lopinavir/ritonavir had an increased risk of preterm birth compared to those receiving the two other ART regimens (Hoffman RN et al., 2019. [PMID 29868833](#)). In a separate study, NIAID-supported investigators reviewed data from a large clinical trial in which HIV-infected women who were treated during pregnancy were randomly assigned to either continue or stop ART after giving birth. The investigators examined the effects on the outcomes of a subsequent pregnancy, including spontaneous abortion and stillbirth but the results were inconclusive, as not all women adhered to the prescribed ART regimen. Further studies are needed to inform decisions on how to balance the relatively low risks of adverse pregnancy outcomes against the benefits of lifelong, uninterrupted ART (Rough K et al., 2018. [PMID 29694825](#)).

### **Risk of Acquiring HIV Increases During and After Pregnancy**

Previous studies have suggested that pregnant women may have a higher risk of HIV infection compared to non-pregnant women. NIAID-supported researchers compared the probabilities of male-to-female HIV transmission per sex act among non-pregnant, pregnant, and postpartum women. Researchers found that a woman's risk of acquiring HIV through sex with a male partner living with HIV increases during pregnancy and is highest during the first 6 months after childbirth, even after considering behavioral factors, such as use of condoms or PrEP. The findings underscore the importance of expanding HIV prevention and testing services for pregnant and postpartum women living in areas with high HIV prevalence and suggest that the physiological changes that a woman's body undergoes during and after pregnancy contribute to an increased risk of acquiring HIV (Thomson KA et al., 2018. [PMID 29514254](#)).

### **High Doses of Anti-HIV Drug Tenofovir Inhibit Wound Healing in Cells of Female Reproductive Tract**

Low effectiveness of PrEP approaches in women, such as intravaginal application of the anti-HIV drug tenofovir, is partially attributed to lack of adherence to the treatment regimen, but other biological or physiological factors may also play a role. For example, the integrity of physical barriers such as the mucous membranes lining the female

genital tract plays a significant role in HIV prevention, and little is known about the process by which the body repairs these tissues and how anti-HIV drugs may affect this process. NIAID-supported investigators assessed whether two related antiretroviral drugs used in PrEP, tenofovir disoproxil fumarate (TFV) and tenofovir alafenamide (TAF), affect wound repair of female reproductive tract tissue from the outermost layer (epithelium) and inner layers (stroma) of the mucosal lining. The results suggest that researchers may wish to consider effects of antiretroviral drugs on wound healing processes in physical barriers to HIV transmission, including the mucosal lining of the female reproductive tract, in future PrEP clinical trials (Rodriguez-Garcia et al., 2017. [PMID 28368028](#)).

## Infectious Diseases other than HIV/AIDS

### **Inflammation Plays Role in Malaria-Related Pregnancy Loss and Premature Delivery**

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. In a study published in 2017, NIAID scientists and their colleagues measured the blood levels of six different cytokines or chemokines—small proteins that are secreted by immune cells and either stimulate or reduce inflammation—from 638 malaria-infected and uninfected pregnant women in Mali. The researchers found that maternal inflammatory immune responses to malaria infection during pregnancy predicted an increased risk of pregnancy loss and preterm delivery. The results emphasize the role of the maternal immune system in influencing pregnancy outcomes during malaria infection and suggest that it may be possible to use blood tests to predict the risk of malaria-associated pregnancy complications (Fried M et al., 2017. [PMID 29020221](#)).

### **Anti-Malaria Antibodies from Mother Protects Infants from Severe Malaria**

Researchers have known for decades that newborns and young infants in sub-Saharan Africa are relatively resistant to malaria infection and severe malaria. Following up on earlier findings, NIAID-funded researchers and their colleagues in NIAID's Laboratory of Malaria Immunology and Vaccinology investigated whether antibodies that target a *P. falciparum* protein called PfSEA-1 are transferred from mother to child during pregnancy, and whether these antibodies are associated with a reduced severity of malaria in the infants. Researchers found that antibodies to a malaria protein, SEA-1, from the mother can confer resistance to severe malaria or death in the offspring. The results also suggest that vaccinating pregnant women with PfSEA-1 could help their infants survive malaria infection (Kurtis JD et al. 2018. [PMID 30165569](#)).

### **Antibody Protects Against Fetal Abnormalities in Mouse Model of Zika Virus Infection**

Zika virus is a mosquito-borne virus that can be sexually transmitted and may cause 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. There is no medicine or vaccine to treat or prevent Zika virus infection. To develop possible therapies for Zika virus infection, NIAID-supported researchers isolated distinct antibodies from immune cells of three people who were previously infected with Zika virus. They found one antibody, ZIKV-117, that neutralized all types of Zika virus tested, including African, Asian, and American strains. Giving a single dose of ZIKV-117 to Zika virus-infected male mice with weakened immune systems up to 5 days after infection protected the mice from death. Additionally, treating pregnant mice with ZIKV-117 before or immediately after infection with Zika virus reduced virus levels in the placenta and in the fetal brain and improved fetal survival and health. This study suggests that ZIKV-117 treatment can reduce transmission of Zika virus from mother to fetus, treat active Zika virus infection, and improve pregnancy outcomes in Zika-infected mice (Sapparapu G et al. 2016. [PMID 27819683](#)).

### **Pregnancy Loss Associated with Zika Virus Infection May Be More Common than Thought**

In a recent analysis, a large team of experts funded in part by NIAID found that fetal death associated with Zika virus occurred in 13 of 50 (26 percent) of the animals studied. Macaques infected early in pregnancy had significantly higher rates of fetal death than those infected after 55 days of pregnancy. The results track with human data showing more severe fetal outcomes in women infected with Zika in their first trimester compared to those

infected later in pregnancy. These findings raise the concern that Zika virus–associated pregnancy loss in humans may be more common than currently thought (Dudley DM et al. 2018. [PMID 29967348](#)).

### **New Clues to Why Influenza Illness Is More Severe in Women than Men**

Influenza virus causes an acute respiratory infection in humans by entering and replicating in lung cells. Each year, seasonal influenza kills between 12,000 and 56,000 Americans and leads to between 140,000 and 710,000 hospitalizations. Pandemic influenza can produce even greater devastation. For influenza infections, studies have shown that females have more inflammation in the lungs in response to influenza infection and overall have a more severe outcome compared to males, despite having comparable levels of influenza virus in the body. This suggests that the worse outcome in females may result from an inability to resolve inflammation rather than a failure in controlling viral replication. To help understand these differences, NIAID-funded researchers evaluated possible sex-based differences in production of a growth factor called amphiregulin (AREG), one of many factors that helps repair and restore the integrity of tissues damaged from inflammation during infection. The researchers found that AREG production was greater in lung tissue and laboratory-grown cells derived from males (both human and mouse) than from females. They further showed that the presence of the male sex hormone testosterone also contributed to the faster recovery of males as compared to females following influenza infection. These findings suggest that AREG and testosterone both contribute to limiting tissue damage from inflammation and mediate faster repair of damaged lung tissue (Vermillion MS et al., 2018. [PMID 30012205](#)).

### **Estrogen Reduces Lung Inflammation and Protects Female Mice from Severe Influenza**

Estradiol (E2) is a form of estrogen known to have anti-inflammatory effects. In an effort to understand the effects of this hormone on influenza-mediated inflammation, NIAID-funded researchers investigated the effects of E2 treatment on influenza infection in mice. They found that treating female mice with E2 reduced total lung inflammation and improved disease outcome following infection with nonlethal doses of IAV. These findings suggest that, although the mechanisms of estrogen-modulated impacts on the course of disease are complex and vary between tissues, overall evidence indicates that estrogen-dependent effects may impact immune responses and provide protective effects during IAV infection (Vermillion MS et al., 2018. [PMID 30032246](#)).

### **Novel Mechanism Identified for Cancer-Promoting Effects of Human Papillomavirus (HPV) Infection**

HPV is the most common sexually transmitted infection and occurs most frequently in resource-limited settings, particularly among those who are younger, female, and infected with HIV. HPV can 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. Certain types of sexually transmitted HPVs, known as high-risk HPVs, cause virtually all cases of cervical cancer and can also cause several other cancers, including anal, head and neck, vaginal, and vulvar cancers. Two of these high-risk viruses, HPV16 and HPV18, are responsible for most HPV-caused cancers. NIAID-supported researchers found that a combination of viral and host-cell DNA sequences drives increased expression of proteins that promote uncontrolled cell division and an accumulation of mutations in infected cells, ultimately leading to cancer. These findings suggest that cancer cells that harbor integrated HPV could ultimately be targeted by therapies that disrupt these host-cell DNA sequences (Warburton A et al., 2018. [PMID 29364907](#)).

### **Brd4 Protein May Be Therapeutic Target for Human Papillomavirus**

HPV replication is complex, involving successive phases in different layers of skin, making it difficult to reproduce and study in the laboratory. To circumvent this problem, NIAID researchers manufactured HPV-like particles, called HPV quasiviruses, which contain the HPV genome packaged inside a viral shell similar to true HPVs. The researchers then used these HPV pseudoviruses to study the importance of the human cell protein Brd4 in the early stages of HPV infection. They infected cells with HPV quasiviruses and found that loss of Brd4 reduced the production of HPV genes and proteins. These results indicate that Brd4 is integral early in the HPV life cycle and may be a promising therapeutic target for developing measures against HPV infection (McKinney CC et al., 2016. [PMID 27879331](#)).

### **Newly Identified Virulence Factor Helps *Listeria monocytogenes* Bacteria Infect the Placenta**



The bacterium *Listeria monocytogenes* (Lm) causes a wide variety of diseases that range from a mild infection of the digestive tract that causes gastrointestinal distress in healthy people to bacterial meningitis, a life-threatening disease that causes swelling of tissues surrounding the brain and spinal cord, in people who have weakened immune systems. Lm is a significant health threat to pregnant women and their unborn children, as infection with this microbe during pregnancy frequently leads to premature delivery and stillbirth. As part of an effort to understand how Lm bacteria overcome the relatively high resistance of the placenta to infection by microbes, NIAID-funded researchers identified the virulence factor InlP, which promoted Lm infection of the placenta in mouse and guinea pig models. Based on these results, InlP may provide a new tool for further study of microbial interactions with the maternal immune system and placenta and could eventually lead to new interventions for the prevention or treatment of infection-related complications in pregnancy (Faralla C et al., 2016. [PMID 27736782](#)).

### **Researchers Characterize Chlamydia Disease Characteristics and Outcomes in Women**

Chlamydia is a common STI caused by infection with *Chlamydia trachomatis* (*C. trachomatis*) bacteria. Chlamydia can have serious consequences in women, including chronic pelvic pain, ectopic pregnancy (pregnancy outside the uterus), and infertility. Researchers commonly use a mouse model to study chlamydia infection of the female urogenital tract and to research potential treatments and vaccines. However, this model exhibits different characteristics depending on which strain of chlamydia is used—*C. trachomatis* or the related mouse strain *Chlamydia muridarum* (*C. muridarum*)—due to differences in factors such as replication, immune response, and protective immunity. In a study published in 2017, NIAID researchers examined *C. trachomatis* and *C. muridarum* infections in mice following surgical removal of their uterus. By studying the different disease characteristics of these strains, researchers may be able to better understand the chlamydia infection process and subsequent outcomes in women and thereby aid the development of treatments and vaccines (Yang C et al., 2017. [PMID 28461392](#)).

## **Immunology and Immune-Mediated Diseases**

### **Immune Responses at the Maternal-Fetal Interface**

NIAID supports research on 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-related problems specific to women, including the impact of pregnancy. In a healthy pregnancy, the mother's immune system accepts, or tolerates, the presence of the developing fetus. Similarly, the fetal immune system does not react against cells from the mother that cross the placenta. Premature or preterm birth can be a sign that there is a breakdown in the maternal-fetal tolerance. While research has shown that maternal immune responses against the fetus can lead to pregnancy complications, not much is known about the role of the fetal immune system in causing complications. To investigate the potential role of the fetal immune system in premature birth, NIAID-funded researchers compared the characteristics of cord blood from preterm and full-term infants. Cord blood from premature infants had elevated levels of inflammation-promoting molecules and a greater activation of immune response-boosting cells called dendritic cells. It also contained immune cells known as T-helper cells, primed to react against molecules from the mother. Finally, cord blood from premature infants also contained many more maternal cells than cord blood from infants not born prematurely. The study findings suggest that an interplay between inflammation, maternal cells that cross the placenta, and aberrant activation of the fetal immune system may play a role in some preterm births (Frascoli et al., 2018. [PMID 29695455](#)).

### **Influenza Vaccine Responses Decline When Administered During Later Stages of Pregnancy**

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. To better understand influenza vaccine responsiveness during pregnancy, NIAID-funded researchers evaluated serum obtained both before and after vaccination from pregnant and nonpregnant women. They showed that the levels of antibody subtypes declined as pregnancy progressed and vaccine responses declined when vaccination occurred later in pregnancy. These results may have implications regarding the optimal timeframe for influenza vaccination of pregnant women (Schlaudecker et al., 2018. [PMID 29941326](#)).

### **Researchers Identify Key Mediators Responsible for Suppressing the Immune Response**

Systemic lupus erythematosus (SLE, or lupus) is a chronic autoimmune disorder that can affect multiple organs and often causes skin rashes, joint inflammation, and pain. Women, particularly women of color and women of child-bearing age, are much more likely than men to develop lupus. Although the causes of lupus are complex and only partially understood, abnormalities in the clearance of apoptotic cells (cells that undergo a programmed cell death process) are thought to be key contributors. Immune cells called macrophages are responsible for safely eliminating apoptotic cells and preventing tissue damage by silencing their inflammatory signals. NIAID-funded researchers recently identified and characterized tissue-specific macrophages that were responsible for removing apoptotic cells and identified the mediators that are essential in silencing the inflammatory response (Roberts et al., 2017. [PMID 29150239](#)).

### **Ritixumab Treatment Affects Replenishment of the B-Cell Repertoire**

Systemic sclerosis (SSc), also known as scleroderma, is a severe and often fatal autoimmune disease marked by hardening of the skin and the connective tissue of internal organs. Women are about four times more likely than men to develop the disease. Patients with SSc often develop difficult-to-treat complications such as a type of increased blood pressure in the lungs known as pulmonary arterial hypertension (PAH). NIAID-supported researchers analyzed blood samples from women receiving rituximab, a synthetic antibody that selectively reduces the number of B cells circulating in the blood, as part of a clinical trial. The researchers found that systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) is associated with abnormalities in B-cell development, particularly in the diversity of antibodies and in the proportions of specific B-cell subtypes. When the researchers examined the dynamics of B-cell depletion during and after rituximab treatment, they found differences between participants in the pattern of B-cell replenishment. They also concluded that the time to repletion after treatment may be a predictable outcome, which could help identify patients who would benefit most from rituximab treatment (de Bourcy et al., 2017. [PMID 28963118](#)).

## **NIH Strategic Plan for Women's Health Research**

The research findings described in this report (see Accomplishments and Activities) support 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 3.4 *Expand research on pregnancy-related conditions such as preeclampsia, diabetes, and hypertension on the subsequent health of women and their offspring.*

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.*

In addition to the reported accomplishments, NIAID also supports scientific programs such as “A Comprehensive Pre-Natal Intervention to Increase Vaccine Coverage” (R01AI110482) to develop, implement, and evaluate an intervention to improve vaccination uptake among pregnant women, which aligns with Goal 3.3, *Encourage research on safe and effective interventions for conditions affecting pregnant women.*

In 2018, NIAID announced a funding opportunity entitled “Immune Mechanisms at the Maternal-Fetal Interface (R01 Clinical Trial Optional)” ([RFA-AI-18-023](#)), which supports research to determine the roles and interactions of immune cells at the maternal-fetal interface throughout pregnancy, including mechanisms of responses to vaccination and infection, that protect or impact the fetus and that may influence fetal immune system development. This initiative maps to Goal 4.2: *Establish new ventures and initiatives with a wide cross-section of partners,*

*including NIH institutes, centers, and offices; academia; other Federal agencies; international organizations; private foundations; and industry.*

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:

- Heightens awareness across NIAID of the importance and substance of women's health 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 research activities
- Coordinates various NIAID-wide presentations on topics such as on safety and effectiveness of hormonal contraceptives in women on ART, malaria vaccine research, and altered immune function during pregnancy.

## Inclusion

Inclusion of pregnant women in clinical research has been a major ethical and practical challenge, and few drug development portfolios include labeling information for use of drugs in pregnant women. The evidence base for clinical practice involving treatment of pregnant women suffers because inadequate safety, dosing, and efficacy studies are conducted in this population. Many pregnant women are undertreated for serious illnesses due to clinician uncertainty about safety of standard regimens. In the HIV context, clinical trials of HIV biomedical prevention options have historically not included pregnant women, even though pregnancy is a critical time of vulnerability to HIV acquisition. In the context of HIV infection, comorbidities such as tuberculosis may be undertreated during pregnancy due to concerns about safety of drug regimens. Despite a long history of using HIV antiretrovirals in pregnancy for interruption of mother-to-child transmission of HIV, newer HIV treatment regimens may also raise safety concerns during pregnancy, as evidenced by recent findings regarding a possible increase in the rate of congenital malformations with the use of the drug dolutegravir.

To address the gaps in inclusion of pregnant women, a NIAID-funded bioethics team is developing ethics guidance for investigators and review bodies to enable responsible and ethical inclusion of pregnant women in research related to HIV/AIDS. As the team develops the guidance, they have conducted critical formative research to understand attitudes, practices, and legal barriers related to inclusion of pregnant women in HIV research. Publications are included in the **References**, and the guidelines for inclusion of pregnant women are nearing completion and will be released in 2019.

## IC STEM Efforts

NIAID supports efforts that align with 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 recently established the AIDS Clinical Trials Group (ACTG) Minority HIV Investigator Mentoring Program (MHIMP) Award to encourage more minority investigators to participate in ACTG research activities. It provides an opportunity for the ACTG network-affiliated clinical research sites to mentor minority junior investigators interested in conducting advanced clinical research in virology, immunology, pharmacology, or other aspects of HIV/AIDS. The goal of the program is to equip the minority investigators to advance to the next level in HIV/AIDS clinical investigation following program completion. NIAID continues to cosponsor the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) mentored career development awards ([RFA-OD-19-020](#)), which support the development of women's health researchers.

NIAID also cosponsors the Research Supplements to Promote Re-Entry into Biomedical and Behavioral Research Careers ([PA-18-592](#)), which aims to encourage individuals to re-enter an active research career after an interruption for family responsibilities.

## Funding Initiatives, Workshops and Conferences

NIAID sponsored a workshop entitled “Multipurpose Prevention Technology Development: Strategies for Addressing the Biomedical, Behavioral, and Regulatory Challenges.” Multipurpose prevention technologies (MPTs) combining prevention of pregnancy and HIV infection have recently emerged as promising next-generation HIV prevention products. Interest in the MPT concept derives from women’s desire to have a single product that would confer both protection from unintended pregnancies and HIV infection, thus potentially increasing product uptake and adherence. This 2-day workshop addressed the complexity of MPT development and proposed a strategy for optimizing the movement of MPTs along a product development pathway that integrates behavioral, social, and regulatory science at the earliest stages to increase the likelihood of getting viable MPTs to market. NIAID also supports an MPT-focused funding opportunity announcement, “Development of Multipurpose Prevention Technologies: A Strategy for the Prevention of Sexually Transmitted Infections (STIs) (R61/R33)” ([RFA-AI-16-085](#)), and made three awards in FY 2018.

In 2018, NIAID announced the funding opportunity entitled “Immune Mechanisms at the Maternal-Fetal Interface (R01 Clinical Trial Optional)” ([RFA-AI-18-023](#)), which supports research to determine the roles and interactions of immune cells at the maternal-fetal interface throughout pregnancy, including mechanisms of responses to vaccination and infection, that protect or impact the fetus and that may influence fetal immune system development.

In December 2016, the Inter-CFAR Collaboration on HIV Research in Women held a symposium hosted by the University of Alabama at Birmingham CFAR, which focused on research in the area of vulnerable populations, microbiome in HIV-infected women and its impact on health outcomes, and the HIV continuum of care across the lifespan of women. More information is available at <http://depts.washington.edu/hivwomen/2016Symposium>.

NIAID continues to participate in several funding opportunities relevant to women’s health and the influence of sex on health and disease. The **Administrative Supplements for Research on Sex/Gender Influences** provides funding for research highlighting the impact of sex/gender in human health and illness. The **U3 Administrative Supplement – Research on the Health of Women of Understudied, Underrepresented and Underreported (U3) Populations** supports research that examines clinical differences among women of diverse racial and ethnic backgrounds, sexual and gender minority women, and women with physical, intellectual and developmental, and/or sensory disabilities. NIAID also participates in **Administrative Supplements for Research on Sexual and Gender Minority (SGM) Populations** that 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 addresses areas beyond HIV/AIDS, including studies on increased disease risk, behavioral and social health, approaches to personalized medicine, access to care, reproductive and sexual development, and resilience.

## Health Disparities

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

- Microbicide Trials Network (MTN)
- HIV Prevention Trials Network (HPTN)
- IMPAACT
- WIHS
- IeDEA
- Inter-CFAR Collaboration on HIV Research in Women
- Sex differences in influenza infection
- Research on STIs including HPV, listeria, and chlamydia

## **Keywords for NIAID Women's Health and Sex/Gender Influences Research (FY 2017-2018)**

**antibody**

**antiretroviral therapy (ART)**

**apoptotic cells**

**autoimmune**

**breastfeeding**

**broadly neutralizing monoclonal antibody**

**Centers for AIDS Research (CFAR)**

**chlamydia**

**cytomegalovirus (CMV)**

**estriol (E3)**

**female genital tract**

**hepatitis C virus (HCV)**

**HIV/AIDS**

**HIV Prevention Trials Network (HPTN)**

**HIV Vaccines Trial Network (HVTN)**

**human papillomavirus (HPV)**

**immunology**

**inflammation**

**influenza**

**International Epidemiology Databases to Evaluate AIDS (IeDEA)**

**International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)**

**Listeria monocytogenes**

**malaria**

**maternal-fetal interface**

**microbicide**

**microbicide trials network (MTN)**

**Plasmodium falciparum**

**postpartum**

**pre-exposure prophylaxis (PrEP)**

**pregnancy**

**preterm**

**Promoting Maternal and Infant Survival Everywhere (PROMISE)**

**sexual and gender minority (SGM)**

**sexually transmitted infections (STIs)**

**systemic lupus erythematosus (SLE)**

**systemic sclerosis (scleroderma)**

**Truvada**

**vaccine**

**vaginal ring**

**Women's Interagency HIV Study (WIHS)**

**Zika virus**

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