NIAID Women's Health Research - Biennial Report (FY 2019-2020)

I. 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 research activities satisfy requirements in the 21st Century Cures Act to include women and minority populations in clinical studies on treatment and prevention of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS), autoimmune diseases, and other diseases. NIAID intramural and extramural researchers continue to analyze data for sex-based differences in basic, translational, and clinical studies and conduct research within NIAID's mission areas that aims to improve women's health and reduce health disparities.

This biennial report provides an overview of selected NIAID-supported research findings relevant to women's health. Sex-based differences in immune responses to infectious disease—including COVID-19, influenza, and methicillin-resistant bacterial infections—have been investigated. Also highlighted are research findings that characterize immune mechanisms during pregnancy, including at the maternal–fetal interface. Women are getting infected with HIV at a higher rate than men, particularly in developing countries, making studies of HIV treatment critical to resolving this public health concern. One such study found that an investigational antiretroviral therapy (ART) in pregnant women with HIV is more effective in suppressing HIV and safer for the infant than a different, commonly used regimen.

In addition to highlighting research that increases our understanding of women's health, this report also features NIAID's activities to support the advancement of women in biomedical careers. Through these efforts and others, NIAID continues its commitment to the inclusion of women in its scientific mission.

II. Scientific Advances

Bacteria Are Selectively Killed by Maternal Immune Cells to Protect the Placenta from Infection

During pregnancy, the mother's immune system dampens in order to accept, or tolerate, the presence of the fetus rather than reject it as something "foreign" in the body. This dampened immune response can make it difficult for a pregnant woman's immune system to prevent an infection from spreading to the placenta and then to the developing fetus. One such infection is caused by the bacterium *Listeria monocytogenes*. Pregnant women are 10 times more likely than other people to get a *Listeria* infection, which can result in miscarriage, stillbirth, premature birth, or serious illness or even death in newborns.

A NIAID-funded study used animal models and cells grown in the laboratory to show that a protein called granulysin is transferred from decidual natural killer cells—a type of immune cell found at the maternal–fetal interface—through a tiny molecular nanotube to *Listeria*-infected placental cells. Once inside the cell, granulysin selectively kills the bacteria by making holes in the bacteria's protective outer membrane without harming the placental cell. This process defends against infection while maintaining tolerance to the developing fetus. These findings, which expand our understanding of reproductive and maternal health, may have broader implications and explain how maternal cells may protect the fetus from other disease-causing microbes (Crespo et al., 2020).

This basic research relates to Objective 1.5 ("Expand research on female-specific conditions and diseases, including reproductive stages, and maternal and gynecologic health") of the Trans-NIH Strategic Plan for Women's Health Research.

Immune Responses to COVID-19 Differ Between Males and Females

There is increasing evidence that men tend to have more severe symptoms of COVID-19 and a higher death rate than women with the disease. To investigate whether there are sex-based differences in the body's immune responses to infection with SARS-CoV-2, the virus that causes COVID-19, a NIAID-funded study enrolled male and female COVID-positive patients admitted to the hospital.

Blood, nasal swabs, and saliva, urine, and stool samples were collected at the time of enrollment and every 3 to 7 days after that. Investigators compared immune responses between patients who recovered and those who progressed to worse stages of disease. Males and females were matched by age, body mass index, and the number of days after their symptoms began.

Several key differences in immune responses were seen between male and female patients with COVID-19. Males had higher blood levels of several inflammatory proteins called cytokines, including two known as IL-8 and IL-18, and lower activation of immune cells called T cells than females, which can recognize and help eliminate invading viruses. The clinical course of COVID-19 in study participants showed that poor T-cell responses in males, but not in females, were associated with progression of disease. Also, T-cell responses declined with age in males only. By contrast, elevated cytokine levels were associated with worse disease outcomes in females but not in males. Together, the results suggest that therapeutic approaches to increasing the T-cell immune responses to SARS-CoV-2 might work best for males, whereas female patients might benefit from therapies that reduce the activation of inflammatory proteins early in disease.

This study investigated the influence of sex and gender on COVID-19 presentation and outcomes and identified a potential immunological basis for the difference in disease outcomes between males and females with the disease. The findings underscore the need to consider distinct treatment strategies for COVID-19 in male and female patients (Takahashi et al., 2020).

This clinical research relates to Objective 1.2 ("Investigate the influence of sex and gender on disease prevention, presentation, management, and outcomes") of the Trans-NIH Strategic Plan for Women's Health Research.

Replenishing Beneficial Bacteria Prevents Recurring Bacterial Vaginosis

Bacterial vaginosis (BV) is inflammation caused by an overgrowth of microorganisms that normally populate a woman's vagina. BV may be uncomfortable or painful, can increase the risk of contracting HIV or other sexually transmitted infections, and is associated with higher rates of premature birth and low birth weight babies in pregnant women. While BV can be cured with antibiotics, achieving a durable cure is difficult, as infection often recurs after antibiotic treatments are completed. A NIAID-supported trial conducted by investigators from the Sexually Transmitted Infections Clinical Trials Group tested whether the administration of LACTIN-V following antibiotic treatment in women with BV could lower the incidence of recurrence. LACTIN-V, an intravaginal live biotherapeutic product, is designed to repopulate the vaginal microbiome with the beneficial bacteria typically found in the vaginas of healthy women.

The trial enrolled 228 women who were diagnosed with BV. Participants first received a 5-day vaginal course of metronidazole antibiotic gel to treat BV and then were randomly assigned to receive either LACTIN-V or a placebo. Researchers took vaginal swabs to track bacteria in the volunteers' vaginal microbiomes at follow-up visits 4, 8, 12, and 24 weeks later. After 12 weeks, volunteers who had received LACTIN-V had significantly fewer recurrences of BV than volunteers who had received placebo. After 24 weeks, 39% of volunteers who had received LACTIN-V experienced recurring BV, while 54% of participants in the placebo group had experienced a recurrence. These findings suggest that LACTIN-V treatment can prevent harmful bacteria from causing BV recurrence, and they expand our knowledge about female-specific conditions and gynecologic health. A larger clinical trial to confirm the results and further investigation into whether LACTIN-V can reduce the risk of sexually transmitted infections and premature birth are warranted (Cohen et al., 2020).

This clinical research relates to Objective 1.5 ("Expand research on female-specific conditions and diseases, including reproductive stages, and maternal and

gynecologic health") of the Trans-NIH Strategic Plan for Women's Health Research.

Tuberculosis Preventive Therapy Poses Greater Risk in Pregnancy than Postpartum in Women with HIV

Tuberculosis (TB) is a leading cause of death worldwide and the leading cause of death for people with HIV. When active TB disease develops during pregnancy or in the weeks after birth, it is associated with poor health outcomes for both the mother and baby. Isoniazid therapy to prevent active TB in people with HIV is generally considered beneficial. However, because pregnant women have previously been excluded from clinical trials of isoniazid preventive therapy, information is lacking about the safety, efficacy, and appropriate timing of this approach in pregnant women with HIV.

A clinical trial expanding research on female-specific conditions and maternal health was conducted by the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) Network, which is co-funded by NIAID. The study enrolled 956 pregnant women with HIV and assigned them to take isoniazid either during pregnancy or 12 weeks after delivery. Both groups of women—those who took isoniazid during pregnancy and those who began taking it 12 weeks after delivery—experienced some poor health outcomes for fetuses and newborns (stillbirth, spontaneous abortion, low birth weight, preterm delivery, and congenital abnormalities). However, the percentage of pregnancies with poor fetal and newborn health outcomes was reduced in the group who began isoniazid after delivery (17%) versus during pregnancy (24%). Thus, for women living with HIV, treatment during pregnancy with isoniazid posed significantly greater risk of poor health outcomes and death for the fetuses and newborns than treatment during the postpartum period. Study investigators noted that this finding is concerning and merits research into alternative approaches to TB preventive therapy in pregnant women (Gupta et al., 2019).

This clinical research relates to Objective 1.5 ("Expand research on female-specific conditions and diseases, including reproductive stages, and maternal and gynecologic health") of the Trans-NIH Strategic Plan for Women's Health Research.

Interruption of HIV Treatment Is Well Tolerated in Women Following Childbirth

Antiretroviral therapy (ART) is used to treat HIV infection by suppressing levels of virus in the body, which can prevent transmission. Interruption of ART can permit HIV transmission or progression of disease. A clinical study examined the safety of interrupting HIV treatment in women following childbirth and compared the results with findings in men to investigate the influence of sex on disease management/outcome and expand research into maternal health.

As part of the NIAID-funded Promoting Maternal and Infant Survival Everywhere (PROMISE) trial, researchers studied the safety of discontinuing ART following childbirth. They also measured the amount of time required for HIV to return to detectable levels in the blood, known as viral rebound. The trial enrolled women with HIV from Africa, Asia, North America, the Caribbean, and South America who were virally suppressed and did not have symptoms of HIV/AIDS. The women were randomly assigned either to continue or to discontinue ART in the period after childbirth. Treatment interruption was well tolerated by study participants, with very few serious adverse health events resulting from viral rebound.

Researchers compared the time to viral rebound of women in this clinical trial with results from another set of studies that enrolled predominantly U.S. male participants, called the AIDS Clinical Trials Group (ACTG). This comparison showed that the virus remained suppressed longer among women participating in the PROMISE study than in men participating in the ACTG study. The results of the PROMISE study suggest that brief interruptions in ART may be well tolerated in women with HIV. In addition, they underscore the importance of considering sex differences in future HIV cure studies. Identifying relevant factors related to cure research that differ by sex will be important for developing effective therapies for all people with HIV (Le et al., 2019).

This clinical research relates to Objectives 1.2 ("Investigate the influence of sex and gender on disease prevention, presentation, management, and outcomes") and 1.5 ("Expand research on female-specific conditions and diseases, including reproductive stages, and

maternal and gynecologic health") of the Trans-NIH Strategic Plan for Women's Health Research.

III. Promotion of Women's Health Research

» ***Sex Differences in Antibody Responses to Various Influenza Strains***
The NIAID Centers of Excellence for Influenza Research and Surveillance (CEIRS) is funding a study of sex differences in immune responses to different strains of influenza, which will help discover basic biological differences between females and males and investigate the influence of sex on disease presentation and outcomes. Using human clinical samples collected in Taiwan and the United States from participants admitted to the hospital with confirmed influenza and at 28 days post-admission, CEIRS investigators will characterize antibody responses that are associated with differing influenza strains and disease severity. Leveraging both the human samples and a mouse model, researchers will test the hypothesis that sex affects intrinsic properties of antibody-producing immune cells, called B cells, to result in differential antibody responses and protection against influenza in females compared with males. This study, funded in 2019, expands on previously funded work that demonstrated that influenza vaccine efficacy is higher in females than males.

This relates to Objectives 1.1 ("Discover basic biological differences between females and males") and 1.2 ("Investigate the influence of sex and gender on disease prevention, presentation, management, and outcomes") of the Trans-NIH Strategic Plan for Women's Health Research.

» ***Sex-Based Differences in Murine Methicillin-resistant Staphylococcus aureus (MRSA) Bacteremia*** (3 U01 AI124319-03)
Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria can cause life-threatening infections. About one-third of MRSA infections are resistant to established MRSA treatment, resulting in the persistent presence of bacteria in the bloodstream, or bacteremia. In an ongoing NIAID-supported study, initiated in 2018, a model of MRSA infection in male and female mice is being used to study new approaches to preventing and treating persistent bacteremia. The data show significantly greater levels of infection in target organs of male mice and less susceptibility to antibiotics in male kidneys and spleens compared with female mice. Importantly, the finding that males are at risk for worsened disease and less antibiotic efficacy appears

to reflect clinical trends seen in human MRSA infection. Further studies are underway utilizing this innovative study design to evaluate the influence of sex on the ability to resolve bacterial infections.

This relates to Objectives 1.2 ("Investigate the influence of sex and gender on disease prevention, presentation, management, and outcomes") and 2.1 ("Expand and develop advanced and innovative approaches for study design, data collection, and analysis to optimize data quality and the ability to detect the influences of sex and gender on health and disease") of the Trans-NIH Strategic Plan for Women's Health Research.

» ***Ongoing Research to Provide Tools for HIV Prevention and Treatment in Women and Adolescent Girls and During Pregnancy***

NIAID continues to support the development of HIV prevention tools, including the dapivirine ring, a vaginal ring that continuously releases the anti-HIV drug dapivirine over the course of 1 month. In July 2020, the European Medicines Agency approved the dapivirine ring for use by cisgender women in developing countries to reduce their risk of HIV infection. This announcement disseminated important information about the increased number of pharmacologic HIV prevention options available to women in sub-Saharan Africa, who are among those most affected by the HIV epidemic. Pre-exposure prophylaxis (PrEP), a single antiretroviral therapy (ART) pill taken daily, is another powerful HIV prevention strategy that could potentially protect pregnant and postpartum adolescent girls and young women from acquiring HIV. A NIAID-supported clinical study, IMPAACT 2009, is assessing whether pregnant and postpartum adolescent girls and young women are willing and able to consistently take daily PrEP and whether it is safe for them and their infants. Early results showed that among participants who took PrEP daily under direct observation, levels of the PrEP drug tenofovir were more than 30% lower in those who were pregnant than in those who had recently given birth, underscoring the critical importance of daily adherence to PrEP for this population. Like prevention of HIV, treatment of pre-existing HIV infection during pregnancy is also complicated because of metabolic changes in the mother and the possibility that therapy will be harmful to the fetus. A large international trial recently demonstrated that ART regimens containing dolutegravir were more effective in suppressing HIV and safer for the infant than a different, commonly used regimen.

This relates to Objectives 1.2 ("Investigate the influence of sex and gender on disease prevention, presentation, management, and outcomes"), 1.5 ("Expand research on female-specific conditions and diseases, including reproductive stages, and maternal and gynecologic health"), 3.1 ("Design and test approaches to promote the adoption, adaptation, and integration of evidence-based interventions in public health, clinical practice, and community settings"), and 3.2 ("Identify collaborative opportunities and leverage partnerships to disseminate research that improves the health of women") of the Trans-NIH Strategic Plan for Women's Health Research.

» ***Clinical Development Plan to Test Malaria Vaccine in Pregnant Women***

Malaria in pregnancy is a major cause of maternal and infant mortality in areas where malaria is endemic. No malaria vaccine candidate has ever been tested in pregnant women. In 2019, NIAID investigators and collaborators in Mali developed a clinical testing site for vaccine studies in pregnant women. As a first step, a study to assess the safety and efficacy of a malaria vaccine candidate, called PfSPZ, in women of child-bearing potential is currently enrolling participants. In this randomized, placebo-controlled clinical trial, researchers will administer the vaccine at 1, 8, and 29 days at two different doses to assess its safety and tolerability in nonpregnant Malian women (ClinicalTrials.gov Identifier: NCT03989102). Women who become pregnant during the study and their infants will be followed to assess maternal clinical outcomes. The next steps in the vaccine clinical development plan are studies of the safety and efficacy of PfSPZ vaccine in all trimesters of pregnancy. This research investigates the influence of sex and gender on malaria prevention, expands research on malaria vaccination during pregnancy, and expands and refines methodologies to improve the recruitment and retention of pregnant women in clinical research.

This relates to Objectives 1.2 ("Investigate the influence of sex and gender on disease prevention, presentation, management, and outcomes"), 1.5 ("Expand research on female-specific conditions and diseases, including reproductive stages, and maternal and gynecologic health"), and 2.4 ("Expand and refine methodologies to improve the recruitment and retention of women underrepresented in clinical research") of the Trans-NIH Strategic Plan for Women's Health Research.

» ***Immune Mechanisms at the Maternal–Fetal Interface (RFA-AI-18-02)***

Eleven projects were awarded in 2019 under the NIAID funding opportunity titled "Immune Mechanisms at the Maternal-Fetal Interface (R01 Clinical Trial Optional)" (RFA-AI-18-023), which aims to support innovative research that uses advanced study designs to determine the roles and interactions of immune cells at the maternal–fetal interface throughout pregnancy. This work includes the study of mechanisms underlying maternal responses to vaccination and infection that protect or impact the fetus and how they might influence fetal immune system development. The funded projects explore a diverse array of key immunological parameters. Several projects focus on developing a better understanding of the immune cells that fight infection, such as uterine natural killer cells, which play a key role in the maternal immune response during pregnancy. Another project will define placental immune responses that are critical for resolution of bacterial infections, while others will investigate factors that alter maternal–fetal sensitivity to viral infections such as hepatitis B virus, Zika virus, rubella virus, and herpesvirus-2. The biological phenomenon of how the fetus and placenta avoid rejection by the maternal immune system will also be explored.

This relates to Objectives 1.5 ("Expand research on female-specific conditions and diseases, including reproductive stages, and maternal and gynecologic health") and 2.1 ("Expand and develop advanced and innovative approaches for study design, data collection, and analysis to optimize data quality and the ability to detect the influences of sex and gender on health and disease") of the Trans-NIH Strategic Plan for Women's Health Research.

IV. Advancement of Women in Biomedical Careers

Women in Immunology: 2020 and Beyond

In February 2020, four female NIH intramural scientists, including two from NIAID, published a perspective article, Women in immunology: 2020 and beyond. Despite the progress that women have made in the field of immunology, challenges to retention and career advancement remain. The authors outlined a three-pronged approach to creating exemplary work environments that allow every female scientist to achieve her fullest potential: (1) equalizing resource allocation, (2) optimizing mentorship and providing advocacy, and (3) challenging stereotypes and beliefs emerging from a patriarchal culture. Their approach aligns with Objective 4.5 of the Trans-NIH Strategic Plan for Women's Health Research ("Promote and support policies, mentoring and networks, collaborations, and infrastructure to retain and advance women in their careers").

The article highlights the critical need to equalize both quantitative and qualitative resources and to have women in leadership positions, as those positions are often responsible for allocating discretionary funds. For effective mentorship and advocacy, women must be models for the younger generation and provide career advancement advice. In addition, both men and women in positions of power must actively promote and advocate for women within their departments. Finally, a change is needed in the criteria by which promotion and advancement are evaluated, as many of these metrics tend to favor males. The authors believe that some of the straightforward changes identified in their article can translate into significant advances for women in science (Pierce et al., 2020).

Bilateral and Multilateral International Programs Support Women in Biomedical Science Careers

NIAID participates in collaborative research funding opportunities and conferences through the East Asia Science and Innovation Area Joint Research Program (e-ASIA-JRP) and the U.S.-Japan Cooperative Medical Sciences Program (USJCMSP). Both programs promote

and foster the inclusion and leadership of diverse women scientists in collaborative biomedical research, which aligns with Objective 4.3 of the Trans-NIH Strategic Plan for Women's Health Research ("Enhance and develop programs to recruit, support, retain, and advance women at all stages of their research careers, from early career to leadership positions").

The e-ASIA JRP supports collaborative research projects that promote and include scientific exchange and capacity building activities. Research project review criteria indicate that each project should conduct activities to engage female researchers where strengthening capacity is needed.

The purpose of the USJCMSP, established in 1965, was to undertake an expanded, cooperative research effort in the medical sciences, concentrating on health problems in Southeast Asia. In their 2016 Declaration of Bethesda, the USJCMSP Joint Committee declared that it would "make a special effort to involve female scientists and other underrepresented groups in USJCMSP activities." Since then, one objective of the USJCMSP Collaborative Awards Program is to encourage the mentoring and training of early-stage and female investigators through collaborations with mid-career and senior investigators in the areas of infectious diseases and immunology. Each collaborative research team must include at least one early-stage or female investigator and requires that either the Japanese sub-team or the U.S. sub-team include an early-stage or female investigator as a primary investigator. Recipients of the USJCMSP Collaborative Awards participate and present their research at the program's annual international conference on emerging infectious diseases.

V. Implementation of the NIH Policy on Sex as a Biological Variable (SABV)

NIAID continues to support research and practices in alignment with the SABV policy:

- In the **NIAID Scientific Review Program**, peer reviewers evaluate the SABV policy's elements in grant applications as one element of the Rigor and Reproducibility policy's four areas of focus (scientific premise, scientific rigor, biological variables, and authentication). For awarded grants, NIAID program officers evaluate compliance with the SABV policy when reviewing yearly progress reports.
- In 2019, NIAID staff participated in the ORWH ***GWAS, Sex, and Chromosomes Think Tank***, helping to identify gaps and opportunities related to genetic association analyses of the sex chromosomes and the consideration of SABV in genome-wide association studies (GWAS).
- NIAID also participates regularly in the **Trans-NIH SABV Working Group**, which is mandated to inform SABV policy development. In 2020, NIAID staff presented to the SABV Working Group on sex and gender influences in coronavirus disease.
- The **Trans-NIAID Women's Health Research Working 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 working group meets quarterly to disseminate information regarding NIH's SABV policy updates and trans-NIAID and trans-NIH collaborations on women's health research activities and to heighten awareness of the importance and substance of women's health research.
- NIAID encourages evaluation of sex-based differences in all research on HIV/AIDS, non-HIV infectious diseases, and immunology and immune-mediated diseases. For example, in FY 2020, NIAID prepared a **notice of special interest (NOSI)** on pan-coronavirus vaccine development program projects to highlight the critical need to develop vaccine candidates capable of providing broad and durable protective immunity against multiple coronavirus strains, especially SARS-CoV-2 and others with pandemic potential. The NOSI, to be published in FY 2021, expresses NIAID's interest in funding highly collaborative, multidisciplinary studies that will investigate vaccine-induced responses across the lifespan, including investigation of age- or sex-related effects on vaccine efficacy.

VI. Inclusion of Women in Clinical Research

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. The **Office of HIV/AIDS Network Coordination Women's HIV Research Collaborative (WHRC)** has successfully promoted the inclusion of cisgender and transgender women in HIV prevention and cure research, with trainings, a statement advocating for the inclusion of women in HIV and COVID-19 research that was signed by 58 individuals and organizations, and an infographic for National Women and Girls HIV/AIDS Awareness Day.

The NIAID **HIV Prevention Trials Network (HPTN) and HIV Vaccine Trials Network (HVTN)** are international clinical trial networks that analyze data for gender differences regarding safety, tolerability, and immune responses to interventions. HPTN develops and tests non-vaccine HIV prevention strategies such as pre-exposure prophylaxis (PrEP). HPTN efforts to develop long-acting forms of HIV prevention include an ongoing study, HPTN 084, comparing the efficacy and safety of injectable cabotegravir with daily oral PrEP (a dose of two antiretrovirals in a single pill) in cisgender women. HVTN is working toward the development of an effective and safe HIV vaccine. HVTN 703/HPTN 081 is assessing the safety and efficacy of a broadly neutralizing monoclonal antibody called VRC01 in reducing acquisition of HIV in cisgender women in sub-Saharan Africa. HVTN 705 (Imbokodo study) is evaluating a vaccine regimen among women and has fully enrolled 2,600 women in southern Africa. HVTN 706 (Mosaico study) is a large international study to test whether an investigational vaccine regimen can safely and effectively prevent HIV among 3,800 cisgender men and transgender individuals, which has enrolled just over 500 participants.

NIAID also promotes the inclusion of women in clinical trials beyond the HIV/AIDS clinical trials networks. The **Vaccine Research Center** Clinical Trials Program strives to enroll a diverse group of participants, including women and underrepresented minorities, in all clinical studies. In a recent study of SARS-CoV-2, the virus that causes COVID-19 (NIAID Protocol #20-I-0083), NIAID investigators engaged an innovative system that recognizes potential needs for increased participation while enrollment is underway to ensure inclusion of women from diverse populations. A SARS-CoV-2 clinical trial funded by NIAID (5U01AI144673-02) is leveraging existing mother–infant cohorts originally established to study influenza to investigate how COVID-19 impacts women's health.

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