

NATIONAL INSTITUTES OF HEALTH
FISCAL YEAR 2003
PLAN FOR HIV-RELATED RESEARCH

X: WOMEN & GIRLS
AND HIV/AIDS

PREPARED BY THE OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Women & Girls and HIV/AIDS

SCIENTIFIC ISSUES

Although relatively few women were diagnosed with AIDS early in the epidemic in the United States, by the end of the 1990s that had changed considerably. According to the Centers for Disease Control and Prevention (CDC), the proportion of AIDS cases reported among women increased from 7 percent in 1985 to 23 percent in 1999. Today, women represent an estimated 30 percent of new HIV infections reported in the United States. Many of those affected are young women and girls, and most are members of racial and ethnic minority communities. Of newly HIV-infected women, approximately 64 percent are black, 18 percent are white, 18 percent are Hispanic, and a small percentage are Asian/Pacific Islander or American Indian/Alaska Native. In 1998, HIV was the third leading cause of death among African-American women ages 25–44 and the fourth leading cause of death among Latinas, compared to the tenth leading cause for white women. In the United States, it is estimated that approximately 75 percent of women with new HIV infections reported in 1999 were infected through heterosexual sex, and 25 percent were infected through injection drug use.

HIV/AIDS affects women of all ages, but it is most prevalent among women in their childbearing years. In 1999, approximately 68 percent of new AIDS cases reported in women in the United States were among those age 30–49. Although girls age 13–19 years represent only 2 percent of new AIDS cases among all women, they represent 58 percent of new AIDS cases in this age group (i.e., 13–19-year-old boys and girls).

Globally, women comprise approximately 47 percent of the over 36 million adults living with HIV/AIDS, according to a UNAIDS report from the end of the year 2000. Forty-one percent of people newly infected with HIV in the year 2000 were women. Most women become infected through heterosexual intercourse, and, in some countries, a significant proportion contract HIV infection through injection drug use. Around the world today, more women than men are dying from HIV/AIDS.

Women experience HIV/AIDS differently than men do in a number of important respects, some of which are physiological and some of which are social. For example, women have a much higher risk than men for contracting HIV through heterosexual intercourse. Women progress to AIDS at lower viral load levels and higher CD4 counts than do men, a finding that might have implications for care and treatment of HIV-infected women, particularly with antiretroviral therapies (ARTs). Additionally, although advances in AIDS medications have reduced AIDS-related mortality in the developed world, women overall have not benefitted from them as much as men have. In the United States, between 1993 and 1998, the number of AIDS-related deaths among women was estimated to have declined by 35 percent, while it declined by 64 percent among men. Women's childbearing capacity also differentiates their HIV/AIDS experiences from men's, as pregnant, HIV-infected women may transmit the virus to their fetuses and infants. Moreover, women in most societies are the primary care providers for children and older people, so when young and middle-aged women die from AIDS and its complications, they often leave dependents with no one to care for them. For all of these reasons, it is important to understand the ways in which sex and gender confer vulnerability to, or protection from, HIV infection and AIDS among women and girls—in general, and relative to men—in diverse geographical settings and during different stages of the life course.

First, there are a host of questions that remain unanswered about specific anatomical and physiological characteristics of women and girls that might play a role in transmission, acquisition, or resistance to HIV infection. Better understanding of the biology of HIV transmission in women and girls requires investigating the molecular basis and chronology of the early steps in the infectious process, including identification of cells susceptible to HIV infection in the lower and upper reproductive tract; the vaginal and cervical ecology; the natural and acquired defense mechanisms at those mucosal sites; and the role of viral load in HIV transmission. Other important factors in HIV acquisition may include the influence of hormonal modulation on viral replication and immune responses in the reproductive tract, and co-factors, such as coincident infections with other sexually transmitted disease (STD) pathogens.

OBJECTIVE:

- **Elucidate biologic determinants (sex and gender) of HIV transmission and define the mechanisms by which viral, host, and immune factors may influence the process of HIV transmission and acquisition among women and girls across the life cycle.**

Once infected, women and girls experience HIV infection and progression to disease in some ways similar and in some ways different from men and boys. Basic mechanisms of viral replication and pathogenesis are not expected to differ in women and men. However, there are differences in the way HIV disease is manifested in women and men. Recent studies have highlighted differences in viral dynamics in women compared with men. HIV viral load has been found to be significantly lower in women than in men at the time of seroconversion; and while plasma viral load at seroconversion predicted progression to AIDS in men, it failed to predict progression in women until 2 years after seroconversion. The implications of these differences for HIV disease progression and treatment are not yet fully understood. These issues and others are being explored in ongoing, natural history, cohort studies, such as the Women's Interagency HIV Study (WIHS) and the HIV Epidemiology Research Study (HERS).

The results of a study in Kenya indicated that women are often infected by multiple variants of HIV, while men are not. This difference was observed early in infection and was found independent of the viral subtype. These data represent another indication that research solely involving men cannot be used to fully understand HIV transmission and pathogenesis in women or to design prevention strategies targeted to women. Further studies should be conducted to determine the importance of early, greater viral diversity in women and the effect those differences might have on disease progression.

Another area of differing disease manifestation between women and men is the metabolic abnormalities and body composition changes associated with HIV infection, disease, and treatment. Although the incidence of wasting has declined as a result of effective ARTs, wasting, which is characterized by weight loss and malabsorption, remains a major cause of morbidity and mortality in individuals who do not respond or lack access to anti-HIV treatment. Women exhibit a disproportionate decrease in body fat relative to lean body mass both at early and at advanced stages of wasting, while men experience a disproportionate decrease in lean body mass and a relative sparing of body fat. Recently, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and abnormal fat redistribution (either depletion or accumulation) have been described in HIV-infected individuals

taking ARTs. In addition to the direct effect of the drugs, the following may play a role in the development of these abnormalities: age, duration of therapy, HIV infection and disease, and return to health following suppression of viral replication. For women, the fat redistribution tends to be away from the face, limbs, and buttocks, and toward breasts and stomachs, an occurrence that is both physically and psychologically upsetting to most women.

There are a number of HIV-related conditions that occur solely or more frequently in women than men. Chief among these are those that relate to gynecological manifestations, especially vulvovaginal candidiasis, pelvic inflammatory disease, and cervical dysplasia. The risk of invasive cervical cancer (ICC) has been found to be five times greater for HIV-infected women than for the general population. HIV-infected women are also at greater risk for cervical human papillomavirus (HPV) infection, which has been associated with cervical cytological abnormalities. Other common HIV disease manifestations among women include oral and esophageal candidiasis, herpes simplex virus infection, and cytomegalovirus infection. Menstrual irregularities are reported frequently by HIV-infected women as well. Additional research is necessary to better understand the biological underpinnings and consequences of these clinical manifestations, as well as their relationships to HIV disease, other co-occurring conditions, and therapeutic interventions experienced by women and girls.

OBJECTIVE:

- **Study the biology of HIV infection, progression to disease, and development and course of clinical manifestations associated with HIV infection, therapeutic interventions, co-infections, and concomitant conditions among women and girls.**

Research findings about differential rates of HIV/AIDS disease progression and death between women and men have focused scientific investigations on sex- and gender-related differences in response to therapy. A key question is whether ART regimens need to be different for women and men. So far, studies have not shown sex-based differences in survival among participants in clinical trials of various antiretrovirals. However, many of these studies have not had sufficient numbers of women to rigorously examine sex differences. Women now constitute about 17 percent of NIH-sponsored clinical trial participants, which is close to their proportion of HIV infection in the United States; but this number may not be large enough to allow for appropriate statistical analysis of gender differences in any one trial.

Current ARTs, alone and in combination, have side effects and toxicities, some of which may be sex-specific. For example, some research suggests that women who take nucleoside analogue reverse transcriptase inhibitors (NRTI) are more likely than men taking these drugs to experience lactic acidosis and hepatomegaly. Studies also have indicated that women are less able to tolerate ddI than are men, and women are more likely to experience severe adverse events, particularly rash, from nevirapine than are men. Further research is necessary to determine the bases of these sex and gender differences in response to therapies.

Many HIV-infected women take antiretroviral medications in combination with other drugs—legal and illicit. There are data to suggest that some antiretroviral agents interact with oral contraceptives, diminishing the effect of the contraceptives, and many women have been counseled to use alternative forms of birth control as a result. Additional research is needed on the potential interactions between ART and medications for opportunistic infections (OIs) and other illnesses, as well as between ART and alcohol and other drugs of potential abuse, such as heroin, cocaine, and methamphetamines.

HIV-infected pregnant women have received a great deal of attention, but this has mostly been focused on their role in preventing transmission to their offspring. Less attention has been given to these women as women. (*Note:* In this section of the Plan, issues of maternal-to-child HIV transmission are included to the extent that the focus is on the pregnant or postpartum woman, rather than the child. More detailed discussions of prevention of perinatal transmission may be found in the Natural History and Epidemiology, Therapeutics, and HIV Prevention Research sections of the Plan.) The preponderance of evidence to date suggests that pregnancy itself does not exacerbate HIV disease progression in women. Currently, there are no major differences in the recommended treatment regimens for pregnant and non-pregnant HIV-infected women, although treatments may be adjusted during different trimesters of a woman's pregnancy. Much remains to be known about the long-term effects of antiretroviral and other treatments on mothers and newborns. Research on the influence of maternal HIV infection on obstetric outcomes has produced mixed conclusions. One study controlling for a number of demographic, disease, and substance use factors did find that HIV-infected mothers were more likely than uninfected mothers to deliver low-birth-weight babies. Another study suggested greater susceptibility to spontaneous abortion among HIV-infected women than uninfected women. All of these issues require further investigation.

OBJECTIVE:

- **Conduct and support research to inform the diagnosis, care, and treatment of HIV-infected women and girls across the life cycle, including clinical studies of therapeutic interventions.**

An understanding of the specific experiences of women and girls in relation to HIV infection and AIDS must go beyond sex differences in infection rates and disease manifestations. There are profound differences in the root causes and consequences of HIV and AIDS in females and males that have to do not only with biology, but also with psychology, cultural attitudes, and social and economic position. In most societies, women and girls hold lower social positions than men and boys, and this situation confers additional vulnerabilities to HIV infection and AIDS. It is important to understand the socially constructed aspects of male and female relationships within various societies, including economic dependence, political decision-making, and access to health, other social services and education, that influence differential health outcomes for women and men.

These relationships play out in individuals' sexual development, sexuality, and sexual behavior, all of which are governed by social and cultural norms, and all of which may influence risk for, or protection from, HIV transmission and acquisition. Much more needs to be understood about gender and the development of sexual identity as they relate to healthy and unhealthy sexual behaviors—and other behaviors related to HIV transmission, such as injection drug use—throughout the life course. These developmental processes must be understood in the context of social arrangements that often are characterized by gender inequality in which women have less power than men. Such power imbalances may extend to intimate relationships between women and men that contribute to women's increased vulnerability to HIV infection. Women and girls may not feel they can safely express their desires to engage in preventive behaviors, and they may be subject to violence and sexual abuse that increases their risk of HIV infection. The impact of culturally influenced gender roles and relationships on sexual and injection drug-using behaviors related to HIV transmission risk and protection is an important area of further study.

OBJECTIVE:

- **Conduct and support basic and intervention research to address the gender-specific, psychological, behavioral, social, environmental, economic, and cultural dynamics that increase or decrease risk for, and protection from, HIV transmission, acquisition, and disease progression among women and girls.**

Improved understanding of the behavioral and social dynamics of sex and gender is essential to the design of effective HIV preventive interventions for women and girls. Such interventions must be not only gender-specific, but also culturally appropriate and acceptable. A number of interventions have been developed and evaluated for different populations of women in the United States and internationally. Most behavioral interventions involve developing a sense of self-efficacy and providing the skills necessary for women to negotiate with men about the use of condoms, particularly male condoms, or to abstain from sexual intercourse. But these approaches are not necessarily appropriate or relevant to some cultural settings, where frank discussions of sex and sexuality and negotiation among women and men are not the accepted norm. Thus, other forms of HIV prevention for women are necessary, in addition to behavioral interventions.

Increasing attention is focused on physical and chemical barrier methods that women and girls can use on their own (i.e., not necessarily requiring negotiation with male partners) during sexual intercourse to protect against HIV transmission and acquisition. The female condom is one such physical barrier method, which so far appears to be desirable to some groups of women and men and not to others (chiefly because of its cumbersome design and administration). Research is underway to test the efficacy of diaphragms and cervical caps—currently used for contraception—for preventing HIV infection and other STDs.

A key focus of current NIH HIV prevention research is the development of safe, acceptable, and accessible chemical barriers known as microbicides, to prevent HIV transmission during sexual intercourse. Many compounds already have been screened and tested, and a number that have shown promise are in various stages of clinical trials. Researchers are addressing such issues as maintenance of normal vaginal pH and flora, ease of use, long-lasting effect, potential adverse effects on sperm and on integrity of mucosal tissue, and behavioral issues related to acceptability and use of microbicides in the context of sexual relationships. (*Note:* Please see the Microbicides Area of Emphasis in this Plan for further details.)

All HIV prevention methods for women must take into account women's reproductive interests. Physical and barrier methods for HIV prevention must be developed with both contraceptive and noncontraceptive properties to allow for the range of women's reproductive choices.

OBJECTIVE:

- **Conduct and support basic and intervention research to develop, test, and evaluate safe and effective technologies and products, including vaccines and chemical and physical barrier methods that are appropriate, acceptable, and accessible to women and girls, for preventing transmission and acquisition of HIV.**

The impact of HIV infection is experienced in many different ways by women and girls throughout the world. Some of the effects are chiefly biological, as described above, and others are more psychological or social, but most effects are interactive.

The psychological impact of HIV infection for women and girls has not been fully investigated. A number of studies have shown that women who receive a diagnosis of HIV infection and/or AIDS experience depression, anxiety, anger, frustration, guilt, shock, fear, blame (of self or others), loss of self-esteem, and extended bereavement, and some even attempt suicide. This psychological stress leads many women and girls to use or abuse alcohol and other drugs. Some studies indicate that women with HIV infection and AIDS have a greater risk of psychiatric disorders, distress, and other mental health problems than do men. For some women, these manifestations are associated with the realization that their only risk factor was the behavior of their male partner (e.g., injecting drug use and/or sex with other partners), and not their own. Other explanations for gender differences in psychological stress relate to women's roles as primary caretakers in families (which may be stressful), women's greater likelihood of being poor, and women's greater likelihood of being victims of abuse, including sexual assault. Most HIV-infected women are of reproductive age, and they must make difficult choices about whether to have children. Such decisions can be the source of significant psychological stress, including that resulting from the social stigma attached to being an HIV-infected pregnant women. Women may also employ different coping skills than men, for example, discussing their problems with close relatives and friends, praying, expressing anger, and engaging in denial.

Studies have shown a relationship between psychological factors and immunity and immune-system-mediated disease. Thus, appropriate mental health interventions should help prevent the further suppression of an HIV-infected woman's immune system by psychological stressors. Attention to alcohol and other drug use is also important in such interventions, which may be individual or group counseling in design.

The HIV/AIDS pandemic also has had a tremendous impact on family and household structure, kin networks, and other social institutions, such as education and the economy, throughout the world. These consequences have been particularly severe for women and girls because of their cultural roles as primary caretakers of family members and their continued economic dependence on, or inequitable relationships to, men. Research is necessary to better characterize these consequences of the HIV/AIDS pandemic and to inform the development of structural and policy-level interventions that can address them effectively.

OBJECTIVE:

- **Conduct and support basic and intervention research on the biological, psychological, social, and economic consequences of HIV/AIDS for infected and affected women and girls.**

One of the key issues in the diagnosis, care, treatment, and prevention of HIV infection for women and girls is access to health care resources. In the United States, research has shown that HIV-infected women encounter more barriers to care than men, and they enter health care services generally at later stages of infection than do men. Because they tend to be poorer and have dependent children, women with HIV/AIDS who are receiving care are nearly twice as likely as men to be covered by Medicaid and half as likely as men to be privately insured. About 20 percent of HIV-infected women are uninsured altogether. A much higher proportion of women than men with HIV infection report postponing medical care for themselves due to such barriers as sickness or lack of transportation. When they do receive care, women with HIV/AIDS fare more poorly than do men on a number of access and quality measures. For example, HIV-infected women are more likely to be hospitalized and use the emergency room, and they are less likely to have received combination antiretroviral therapy than are men.

In the United States, health care providers are not talking to women about their HIV risks and opportunities for prevention. Studies indicate that less than half of all women, regardless of HIV serostatus, report talking to their health care providers about HIV/AIDS, the risks of HIV infection, or HIV testing. Clearly, much of the important prevention and treatment information about HIV/AIDS in women is not being appropriately disseminated or integrated into other venues where women and girls seek health care services, such as family planning and STD clinics. Early diagnosis of HIV infection is essential for enhancing early prevention and treatment options for women and girls. It also assists them in making informed reproductive choices.

OBJECTIVE:

- **Identify and address the factors that influence women's and girls' access to and experience of HIV/AIDS-related research, care, support, treatment, and prevention services.**

As attention to women and girls increases in HIV/AIDS research, it is imperative to address resource and ethics issues that may be specific to them. This includes appropriate representation of women not only as participants in research studies, but also as the scientists who conduct the studies, both in the United States and internationally. Thus, both research training in the area of women and HIV/AIDS, and training more women as AIDS researchers generally are necessary.

As studies involving women and girls are conducted throughout the world to grapple with the range of HIV/AIDS issues they face, a number of political and ethical issues will have to be addressed. Many laws and policies in various societies related to the status of women and girls (e.g., marriage, divorce, and property rights) have an impact on the participation of females in research. For example, in some societies, a husband's consent is legally required for a woman to participate in a clinical study; the woman cannot provide consent by herself. Similarly, different societies have different rules about the participation in research of pregnant women and girls who are minors, which will affect their ability to participate in studies that may benefit them. As we attempt to increase cross-cultural and international HIV/AIDS research collaborations, which is necessary for combating the pandemic, it is imperative to address these issues.

OBJECTIVE:

- **Conduct and support research, training, and education on ethical issues specifically affecting women and girls in HIV/AIDS-related clinical, behavioral, epidemiological, and health care services research in different cultural settings.**

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE:

Elucidate biologic determinants (sex and gender) of HIV transmission and define the mechanisms by which viral, host, and immune factors may influence the process of HIV transmission and acquisition among women and girls across the life cycle.

STRATEGIES:

- Evaluate HIV transmission and acquisition in relation to viral factors, such as genotype, phenotype (inclusive of drug-resistance), clade, viral load, replicative forms, viral fitness, and heterogeneity.
- Identify and characterize cells responsible for viral acquisition and propagation at mucosal surfaces in the oral cavity and the entire reproductive tract (fallopian tubes, uterus, cervix, vagina, vulva) and anal canal.
- Evaluate HIV transmission and acquisition in relation to viral shedding in different mucosal compartments (including semen, cervicovaginal secretions, and saliva).
- Evaluate HIV transmission and acquisition in relation to age, timing, and occurrence of endocrine status changes (pre-menarche, menarche, postmenarche, pregnancy, pre-menopause, menopause, and postmenopause); the exogenous use of hormones for contraception, ovulation induction, and hormone replacement should be included.
- Evaluate HIV transmission and acquisition in relation to various infectious factors, such as STDs and pre-existing local/systemic infections with other microbial agents, especially as they impact on oral-vaginal microflora.
- Evaluate HIV transmission and acquisition in relation to host genetic factors that influence susceptibility and resistance to infection.
- Evaluate HIV transmission and acquisition in relation to other host factors, such as nutrition, nonhormonal contraception use, anatomic/physiologic changes (female circumcision, cervical ectopy, postdysplasia treatment), and localized inflammation secondary to intrauterine device (IUD) use or local vaginal therapies, douches, or use of vaginal astringents.

- Study the normal biology of the systemic and mucosal immune system (innate and adaptive) in women and girls.
- Define how genetic, infectious, and endocrine factors alter local and systemic immune responses and impact on HIV acquisition and transmission.
- Study the impact of effective ARTs on women's genital tract viral dynamics (including the development of resistance) and vertical and sexual HIV transmission.
- Investigate the influence of autoimmune diseases on transmission and acquisition of HIV.
- To facilitate the research goals listed above:
 - ▶ Develop standardized assays for immune response and viral load in genital tract and oral samples;
 - ▶ Develop noninvasive procedures for genital tract sampling; and
 - ▶ Promote studies in animal models to explain host-viral-immune factors involved in HIV transmission and acquisition.

OBJECTIVE:

Study the biology of HIV infection, progression to disease, and development and course of clinical manifestations associated with HIV infection, therapeutic interventions, co-infections, and concomitant conditions among women and girls.

STRATEGIES:

- Elucidate the unique mechanisms mediating virus-host interactions in HIV disease progression among women and girls.
 - ▶ Evaluate HIV viral dynamics and replication in blood and at the tissue level and immune function among women and girls.
 - ▶ Determine normative values for immune parameters including total lymphocyte number, subset composition, and immune cell turnover and distribution.
 - ▶ Investigate the role of potential co-factors and mediators of disease progression in both early- and late-stage disease, including hormonal endogenous (inclusive of hormonal changes across the life cycle and throughout the menstrual cycle) and exogenous (inclusive of hormonal contraception and hormonal replacement therapy) factors; pregnancy, and autoimmune diseases.
 - ▶ Investigate the role of potential co-factors and mediators of disease progression in both early- and late-stage disease, including infectious agents such as hepatitis C virus (HCV) and STDs, re-exposure to different strains of HIV including drug-resistant strains, age, intermittent therapy and monotherapy for perinatal transmission, and genetic factors.
 - ▶ Investigate the role of potential co-factors and mediators of disease progression in both early- and late-stage disease, including nutrition, biological indicators of stress, drug use, and complementary and alternative medicine therapies, including herbal therapies and nutritional supplements.
- Develop approaches for identifying, recruiting, enrolling, and retaining recently exposed and newly HIV-infected women and girls for studies on the pathogenesis of early HIV infection.
- Elucidate the unique etiologies and pathogenic mechanisms of disease manifestations in HIV-infected women and girls.

- ▶ Investigate HIV- and therapy-associated metabolic and body composition changes that may be operative at various stages of infection and disease, to include fat redistribution, bone density, menstrual function, impact on fertility and sexual function, and cardiovascular disease.
- ▶ Conduct studies on the gynecologic manifestations and identification and treatment of gynecologic disease in HIV-infected women and girls.
- ▶ Elucidate gender-specific characteristics of OIs and co-infections in HIV-infected women and girls.
- ▶ Elucidate gender-specific characteristics of HIV-related malignancies, including female-specific cancers.
- ▶ Investigate impact of co-morbid conditions on HIV-related manifestations in women and girls including HCV co-infection and autoimmune disease.
- ▶ Elucidate gender-specific characteristics of neurologic and neuropsychologic (dementia, changes in cognitive function) manifestations of HIV infection/disease in women and girls.
- ▶ Investigate clinical manifestations related to HIV and HIV-related therapies in pregnant and postpartum women including toxicity (e.g., lactic acidosis, hyperglycemia) and postpartum/peripartum morbidity in HIV-infected women undergoing vaginal or operative delivery.
- Evaluate the impact of HIV and HIV-related therapies on breast-feeding.

OBJECTIVE:

Conduct and support research to inform the diagnosis, care, and treatment of HIV-infected women and girls across the life cycle, including clinical studies of therapeutic interventions.

STRATEGIES:

- Evaluate innovative and rapid testing strategies in a range of settings to identify HIV infection in women and girls.
- Study the psychosocial impact of receiving HIV-positive results on women across the lifespan.
- Assess treatment regimens among women who are treatment-experienced.
- Evaluate the impact of antepartum treatment on natural history of disease and development of viral resistance.
- Enhance efforts to evaluate new and existing therapies across all stages of women's lives.
- Study factors affecting adherence to HIV therapeutic regimens across the lifespan, and develop and evaluate interventions designed to improve adherence to HIV therapy.
- Evaluate effects of psycho-pharmacological medications/therapy on women's participation in health care, clinical trials, and adherence to treatment.
- Support research and development of clinical trial designs and statistical methodologies to evaluate clinical efficacy and reasons for failure of anti-HIV treatments, including consideration of optimal time to initiate treatment, treatment interruptions and treatment cycling, treatment in pregnancy, and surrogate markers.
- Investigate interactions of HIV/OI therapies and drugs for other illnesses, including those that affect women solely, disproportionately, and differently from men.
- Study optimal diagnosis and treatment of co-morbidities in women with HIV.
- Evaluate the interaction of mental health therapies and anti-HIV therapies on the course of disease progression.

- Evaluate short- and long-term toxicity, pharmacokinetics, and antiretroviral activity of therapeutic agents in women across the lifecycle, including pregnancy.
- Investigate drug/treatment interactions, including therapies for OIs, illnesses specific to women, hormonal treatments, substances of abuse, complementary and alternative medicine therapies, and (standard) anti-HIV medications.
- Evaluate the long-term effects of anti-HIV therapy on morbidity and mortality among girls and women across the life cycle.

OBJECTIVE:

Conduct and support basic and intervention research to address the gender-specific, psychological, behavioral, social, environmental, economic, and cultural dynamics that increase or decrease risk for, and protection from, HIV transmission, acquisition, and disease progression among women and girls.

STRATEGIES:

- Examine the impact of population-level interventions—such as social normative behavior changes, economic opportunities for women, mass or syndromic approaches to STD control, early diagnosis and treatment of HIV infection and other STDs, and use of family planning programs to diagnose and treat STDs—on HIV transmission and acquisition.
- Support research that explores the impact of risk perception on women’s and girls’ decision making about sexual activity, including decisions about pregnancy.
- Support research to enhance healthy sexual development and protective behaviors (including access to and use of barrier methods, avoidance of too-early or nonconsensual sex, and abstinence from unsafe sexual behavior) among girls and women.
- Study how HIV-related risk and protection might change over time as a function of developmental and life-course events, such as adolescence, childbearing, sexual partnership choice and change, and aging.
- Develop, implement, and evaluate interventions for populations that are currently perceived as low risk for HIV infections, such as sexually active middle-aged and older women, women and girls with physical and mental disabilities, women who have sex with women, lesbian and bisexual women and girls, rural girls and women, Asian Pacific Islanders, Native Americans, and Alaskan Natives.
- Develop, implement, and evaluate culturally focused outreach and peer-based HIV prevention interventions that address risk behaviors and related perceptions among women and girls.
- Develop, implement, and evaluate culturally focused HIV prevention interventions targeting populations of women and girls that face vulnerable and/or isolating circumstances (e.g., incarceration, refugees, sexual exploitation, trauma histories, interpersonal violence, war, homelessness, runaways, gang membership, alcohol and substance abuse).

- Support multidisciplinary HIV research that investigates the bio-behavioral and socio-behavioral determinants and mechanisms of sexuality, including processes of sexual and gender identity formation among girls and women.
- Support research to improve translation of effective culturally focused behavioral and social science-based preventive interventions to communities and health care and prevention service providers serving women and girls.
- Develop, implement, and evaluate partnership issues regarding increased and decreased risk of HIV infection (e.g., dating, relationship violence, power in relationships, and economic survival sex).
- Study the impact of macro events (natural disasters, historical, trauma, war, etc.) on women and girls' HIV risk.
- Support HIV research that addresses the genesis, impact, and elimination of stigma and discrimination among stigmatized and/or historically oppressed groups.
- Support HIV research focused on community-level factors (social, cultural, gender norms and ideologies) that increase or decrease HIV risk of transmission and acquisition among women and girls.
- Identify cultural risk and protective factors (enculturation, acculturation, cultural resilience, spirituality, re-traditionalization, identity) for women and girls.

OBJECTIVE:

Conduct and support basic and intervention research to develop, test, and evaluate safe and effective technologies and products, including vaccines and chemical and physical barrier methods that are appropriate, acceptable, and accessible to women and girls, for preventing transmission and acquisition of HIV.

STRATEGIES:

- Support the discovery, development, and preclinical evaluation of new, improved, acceptable, effective, and safe chemical and physical barrier methods, including topical microbicides and other methods, to reduce sexual transmission of HIV and STDs among women and girls.
- Support the evaluation of existing chemical and physical barriers to reduce sexual transmission of HIV and STDs among women and girls.
- Support the evaluation of the contraceptive efficacy of chemical and physical barrier methods and how this affects acceptability for use in HIV prevention.
- Identify populations of women and girls in the United States and elsewhere with HIV incidence levels suitable for recruitment into vaccine and other HIV prevention intervention trials.
- Develop and evaluate methods to access, recruit, and retain women and girls for preventive intervention studies (including racial/ethnic minorities, adolescents, substance users, and the mentally ill), who are demographically representative of the populations at risk for HIV infection.
- Develop and assess the effectiveness of utilizing multiple prevention approaches, both individually and in combination, that may decrease HIV transmission among women and girls.
- Develop and evaluate biomedical and behavioral interventions for managing STDs (including mass treatment or syndromic approaches) as a potential means of preventing HIV transmission and acquisition.
- Investigate candidate vaccines and other biomedical prevention strategies both in human subjects and in animal models of HIV infection with attention to factors particularly relevant to use in women and girls, such as changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormonal replacement therapy, and presence of selected STDs.

- Study potential effects of candidate vaccine or microbicidal products on the genital tract immune system and their ability to induce inflammatory activity that might compromise the integrity of the mucosal surface of the genital tract and decrease or enhance the inductive ability of vaccines.
- Study the impact on maternal morbidity and mortality of biomedical interventions to prevent maternal to child transmission, including caesarean section.
- Support research to improve translation, dissemination, and increase adoption of effective prevention technologies by communities, and to health care and prevention service providers who serve women and girls.
- Develop and evaluate cost-effective, safer drug-use paraphernalia, such as single-use needles and disposable, safer injection kits to decrease HIV transmission and exposure.
- Develop and evaluate innovative ways to obtain fully informed consent for participation in HIV prevention trials, and document critical aspects (e.g., procedures, risks, benefits, voluntary nature, confidentiality, etc.).
- Support research to identify barriers to enrolling girls who are under 18 years of age in prevention trials and to develop strategies for overcoming these barriers.

OBJECTIVE:

Conduct and support basic and intervention research on the biological, psychological, social, and economic consequences of HIV/AIDS for infected and affected women and girls.

STRATEGIES:

- Conduct multidisciplinary research to understand the synergistic effects of pre- and co-morbid psychosocial conditions more prevalent among women (e.g., depression, trauma) and HIV-related disease progression, and the mechanisms underlying these effects; and develop interventions to enhance physical and mental health outcomes.
- Develop and evaluate interventions that target HIV sero-discordant couples to prevent infection (of HIV and other STDs) and to promote coping and quality of life.
- Support research to understand the consequences of HIV infection and disease progression on women's and girls' sexual and reproductive health and decision making.
- Examine the association between gender-specific psychosocial consequences and HIV-related treatment initiation and maintenance.
- Develop and evaluate interventions to reduce the social and economic vulnerability of female-headed households (e.g., as a consequence of HIV/AIDS-related disease, death, or abandonment), particularly those headed by girls.
- Develop and evaluate interventions to reduce adverse psychological social and economic consequences for women and girls infected or affected by HIV/AIDS, such as those that preserve educational and economic opportunities for girls orphaned by the epidemic, safeguard access to care, provide housing and employment for women, and protect them from violence and abuse.
- Conduct basic research to understand the dynamics of gender-specific stigma/discrimination associated with HIV/AIDS and to inform the development of structural interventions to reduce HIV/AIDS-associated stigma.

OBJECTIVE:

Identify and address the factors that influence women's and girls' access to and experience of HIV/AIDS-related research, care, support, treatment, and prevention services.

STRATEGIES:

- Support research to understand how the organization, financing, management, access, delivery, cost-effectiveness, and cost-utility of health care, reproductive health, family planning, and social services affect women's and girls' HIV risk behaviors, HIV transmission, access to appropriate care, support, treatment, and prevention services.
- Support research to understand and identify effective strategies for the linkage, coordination, and integration of primary medical care; drug, alcohol, and mental health treatment; STD treatment; reproductive health and family planning services; social services; and community-based HIV care, support, treatment, and prevention services, and their effects on women and girls.
- Encourage studies to identify and understand the unmet needs of women and girls for care, support, treatment, and prevention services.
- Support research to understand the impact of policy and policy change—such as health care, health sector reform, health financing systems, legislation, and regulations—on the delivery and utilization of HIV-related services, HIV risk behavior, and HIV transmission among women and girls.
- Encourage multidisciplinary research to elucidate for women and girls barriers to achieving optimal care support, treatment, and prevention service relationships.
- Support research on economic, social, and emotional implications for women and girls who provide support and care to persons with HIV/AIDS.
- Support research to study and address factors that influence the full participation of women and girls in HIV/AIDS-related research.
- Support research on effective strategies for disseminating products, findings, and information from HIV/AIDS-related research to women, girls, and their communities.

OBJECTIVE:

Conduct and support research, training, and education on ethical issues specifically affecting women and girls in HIV/AIDS-related clinical, behavioral, epidemiological, and health care services research in different cultural settings.

STRATEGIES:

- Develop and evaluate efforts to educate potential trial participants about ethical and human rights issues in human research in advance of recruitment, with the goal of obtaining fully informed and free consent among communities.
- Investigate the unintended consequences of policies and practices (including research practices) that provide special benefits to HIV-infected—as compared to uninfected—women and girls (e.g., preferential treatment, health care benefits, access to medications, etc.). Conduct research to examine and determine the contexts and factors that influence when the consent process is being fully voluntary and is an informed aspect of the consent process.
- Support studies to determine whether research benefits the communities from which the participants are drawn.
- Investigate unintended harms and benefits that research participants, their families, and the community accrue as a result of participating in a study.
- Examine the ethical risks and benefits of studies that involve treatment versus observation of women and girls.
- Support research to determine appropriate standards of care that takes into account culture, economic status of participants and communities, reproductive status, religious norms, age, and laws.
- Investigate the ethical impact of studies in which the trial provides the only access to therapeutics within a community.
- Support research on laws, policies, and regulations that inhibit or serve as a detriment to HIV prevention, care, support, and treatment among women and girls. Examples of these would include laws and policies governing marriage, divorce, property, migration, disclosure of HIV infection, etc.

- Assess any negative consequences for women and girls of conducting community-level epidemiological research.
- Study the ethical issues related to diagnostic and therapeutic strategies during pregnancy and lactation.
- Study the ethical issues related to breast-feeding and its alternatives.
- Study the ethical issues related to participation of women and girls in clinical trials.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIHES	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

FY 2003 OAR
Planning Group for
Women & Girls and
HIV/AIDS

FY 2003 WOMEN & GIRLS AND HIV/AIDS PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
AVEG/HVTN	AIDS Vaccine Evaluation Group/HIV Vaccine Trials Network
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CBO	community-based organizations
CDC	Centers for Disease Control and Prevention
CFAR	Centers for AIDS Research
CIPRA	Comprehensive International Programs in Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocytes
DC	dendritic cell
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOT	directly observed therapy
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GI	gastrointestinal

GLP/GMP	good laboratory practices/good manufacturing production
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCFA	Health Care Financing Administration
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpes virus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IHS	Indian Health Service
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpes virus
LRP	Loan Repayment Program, NIH
MAC	<i>Mycobacterium avium</i> complex
MCT	mother-to-child transmission
MDR-TB	multiple drug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organizations

NHL	non-Hodgkin's lymphoma
NHP	non-human primate
NIH	National Institutes of Health
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PHS	Public Health Service
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trials
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	Structured Treatment Interruption
TB	tuberculosis
TI	treatment interruption
UNAIDS	United Nations Joint Programme on AIDS
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study

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