

CHAPTER 5

Research Related to Specific Populations

Women and Girls

Racial and Ethnic Populations

Research in International Settings

Women and Girls

AREA OF EMPHASIS

Women and Girls

SCIENTIFIC OBJECTIVES AND STRATEGIES**OBJECTIVE—A: *Determinants of HIV Transmission***

Elucidate biologic determinants of HIV transmission and define the mechanisms by which viral, host, and immune factors may influence the process of HIV transmission, acquisition, and resistance to infection among women and girls across the life cycle. Study how or whether these determinants differ from those in men.

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, and 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, acquisition, and resistance to infection in relation to age, timing, and occurrence of endocrine status changes (premenarche, menarche, postmenarche, pregnancy, premenopause, menopause, and postmenopause); the exogenous use of hormones for contraception, ovulation induction, and hormone replacement should be included.
- Over all age ranges, evaluate HIV transmission and acquisition in relation to normal vaginal (and oral) microflora and various infectious factors, such as sexually transmitted infections (STIs) and preexisting local/systemic infections with other microbes.
- Evaluate HIV transmission and acquisition in relation to host genetic factors that influence susceptibility and resistance to infection.
- Elucidate mechanisms of innate immunity and other cellular factors affecting acquisition of and resistance to HIV infection.
- Evaluate HIV transmission, acquisition, and resistance to infection in relation to other host factors, such as nutrition, nonhormonal contraception use, anatomic/physiologic changes

(female circumcision, cervical ectopy, and postdysplasia treatment), and localized inflammation secondary to use of intrauterine devices, local vaginal therapies, douches, or vaginal astringents.

- Study the biology of the systemic and mucosal immune system (innate and adaptive) in women and girls and the impact of HIV infection.
- Define how genetic, infectious, and endocrine factors alter local and systemic immune responses and the impact on HIV acquisition, transmission, and resistance to infection.
- Study the impact of effective antiretroviral therapies (ARTs) on genital tract viral dynamics (including the development of resistance) and vertical and sexual HIV transmission.

To facilitate the research goals listed above:

- Develop standardized assays for immune response and viral load, as well as other relevant parameters, 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, acquisition, and resistance to infection.

OBJECTIVE–B: *Biomedical Prevention Interventions*

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 STIs among women and girls.
- Support the evaluation of existing chemical and physical barriers to reduce sexual transmission of HIV and STIs among women and girls.
- Support the evaluation of the contraceptive efficacy of chemical and physical barrier methods and how the efficacy affects acceptability for use in HIV prevention.
- Identify populations of women and girls with HIV incidence levels suitable for recruitment into vaccine, microbicide, and other HIV prevention intervention trials.
- Develop and evaluate methods to access, recruit, and retain women and girls who are demographically representative of the populations at risk for HIV infection for preventive intervention studies (women and girls to include racial/ethnic minorities, adolescents, substance users, and the mentally ill).
- Develop and assess the effectiveness of utilizing multiple prevention approaches, including biologic, behavioral, and community-level strategies both individually and in combination, that may decrease HIV transmission among women and girls.
- Develop and evaluate biomedical and behavioral interventions for managing STIs (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, pregnancy, and menopause, hormonal changes during pregnancy and menopause, the use of contraceptives or hormonal replacement therapy, and the presence of selected STIs.
- Study potential effects of candidate vaccine or microbicial products on the genital tract immune system and mucosal integrity, and the ability of these agents 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 and the efficacy of microbicides.

- Study the impact of biomedical interventions to prevent mother-to-child transmission, including caesarean section, on maternal morbidity and mortality.
- Support research to improve translation and dissemination and increase adoption of effective HIV prevention technologies by communities and by health care and prevention service providers who serve women and girls.
- Develop and evaluate innovative ways to obtain culturally and age-appropriate fully informed consent for participation in HIV prevention trials, and document critical aspects of informed consent (e.g., procedures, risks, benefits, voluntary nature, confidentiality, etc.).
- Study the impact of prevention interventions directed at males on the prevention of HIV and STIs in females.
- Support research to identify barriers to enrolling girls under 18 years of age in HIV prevention trials and to develop strategies for overcoming these barriers, including hard-to-reach populations such as girls living outside of family care, girls involved in the juvenile justice system, and substance abusers.

OBJECTIVE–C: *Behavioral Interventions*

Conduct and support basic and intervention research to address the female-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 across the life cycle.

STRATEGIES

- Examine the impact of population-level interventions on HIV acquisition and resistance to infection among women and girls, such as social normative behavior changes, programs to increase educational opportunities and economic independence, mass or syndromic approaches to STI detection and control, early diagnosis and treatment of HIV infection and other STIs, use of family planning programs to diagnose and treat STIs, and availability of and access to substance abuse treatment.
- Support research across the life cycle that explores the impact of HIV risk perception on sexual activity decisionmaking, including decisions about pregnancy.
- Study how HIV-related risk and protective behaviors might change over time as a function of developmental and life-course events, such as adolescence, childbearing, sexual partnership choice and change, HIV treatment, menopause, and loss of family, social, and economic support.
- Support female-focused intervention research to prevent HIV acquisition through enhanced healthy sexual development and development of protective behaviors across the life course.
- Develop, implement, and evaluate biologic and behavioral interventions that address partnership issues regarding increased and decreased risk of HIV infection (e.g., dating, relationship violence, power in relationships, drug use, and economic survival sex).
- Develop innovative prevention strategies targeting male partners whose behaviors confer risk of HIV transmission to female partners, particularly in populations/areas with elevated HIV prevalence.
- Develop, implement, and evaluate culturally focused outreach and peer-based HIV prevention interventions that address risk behaviors and related perceptions of risk.
- Develop, implement, and evaluate prevention interventions for populations perceived to be at low risk for HIV infection, such as sexually active middle-aged and older women, college students, those with physical and mental disabilities, bisexual women and girls, women and girls residing in rural areas, Asian/Pacific Islanders, Native Americans, and Alaska Natives.
- Develop, implement, and evaluate culturally focused HIV prevention, treatment, and care interventions targeting populations of women and girls at risk due to vulnerable and/or isolating circumstances (e.g., orphaned, incarcerated, refugees, sexual exploitation, trauma, violence, war, homelessness, runaways, gang membership, and alcohol and substance abuse).

- Support research to improve translation of effective culturally focused behavioral and social science-based HIV prevention, treatment, and care interventions to communities and health care and prevention service providers serving women and girls.
- Study the impact of macro events (e.g., natural disasters, trauma, and war) on HIV risk for women and girls nationally and internationally.
- Support HIV research focused on community-level factors (social, cultural, and gender norms and ideologies) that increase or decrease risk of HIV transmission and acquisition among women and girls.

OBJECTIVE–D: *Biology of HIV Disease*

Study the biology of HIV infection, progression to disease, and development and course of clinical manifestations associated with HIV infection, coinfections, and concomitant conditions among women and girls across the life cycle. Study how or whether sex dimorphisms in HIV infection occur.

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 and the impact of HIV infection on those normative values across the life cycle.
 - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including endogenous and exogenous hormonal factors (inclusive of hormonal changes across the life cycle, the menstrual cycle, hormonal contraception, and hormonal replacement therapy), pregnancy, and autoimmune diseases.
 - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including infectious agents such as hepatitis C virus (HCV) and STIs, reexposure 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 cofactors and mediators of disease progression in both early- and late-stage disease, including nutrition, biological indicators of stress, drug and alcohol use, concurrent medication use, and complementary and alternative medicine approaches, 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 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 changes in fat distribution, bone density, menstrual function, fertility and sexual function, and cardiovascular disease.
 - ▶ Conduct studies on the manifestations of gynecologic disease and the efficacy of disease treatment in HIV-infected women and girls.

- ▶ Elucidate characteristics of opportunistic infections (OIs) and coinfections in HIV-infected women and girls.
- ▶ Elucidate characteristics of HIV-related malignancies, including female-specific cancers.
- ▶ Elucidate cofactors (e.g., host genetic and environmental changes) that mediate viral diseases (human papillomavirus [HPV], Epstein-Barr virus [EBV], human herpesvirus type 8 [HHV-8], hepatitis B virus [HBV], and HCV) that are associated with cancers among women and girls with HIV infection.
- ▶ Investigate the impact of infectious comorbidities on HIV-related manifestations in women and girls, including HCV coinfection, and sexually transmitted infections such as HPV and herpes simplex virus (HSV-2), and examine the impact of autoimmune disease.
- ▶ Elucidate characteristics of neurologic and neuropsychologic manifestations (e.g., dementia and changes in cognitive function) of HIV infection/disease in women and girls, including the role of potential cofactors such as substance abuse, mental health disorders, HCV infection, syphilis, and preexisting neurological conditions.
- ▶ Investigate clinical manifestations related to HIV and HIV-related therapies in pregnant and postpartum women, including toxicity (e.g., lactic acidosis and hyperglycemia) and peripartum/postpartum morbidity in HIV-infected women undergoing vaginal or operative delivery.
- Evaluate the impact of HIV and HIV-related therapies on breastfeeding.
- Explore further the role of pharmacogenetic factors as explanations for variations in HIV disease course.

OBJECTIVE–E: *Treatment of HIV Disease*

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, in order to define optimal treatment strategies for females.

STRATEGIES

- Evaluate innovative and rapid testing strategies in a range of settings to identify HIV infection in women and girls.
- Assess novel case-finding approaches, including social- and risk-network-based strategies to identify undiagnosed HIV infection among women and girls and to identify women at risk for HIV infection.
- Study the psychosocial consequences of receiving HIV-positive results on women across the lifespan, including during adolescence, during the reproductive years, and during menopausal and postmenopausal stages of life, and the impact on treatment and care decisionmaking and reproductive decisionmaking.
- Evaluate the impact of antepartum and intrapartum HIV treatment on the natural history of disease and development of viral resistance.
- Enhance efforts to evaluate the efficacy and effectiveness of new and existing therapies and therapeutic regimens across the life cycle, in both treatment-naïve and treatment-experienced women and girls.
- Study factors affecting adherence to HIV therapeutic regimens across the lifespan, and develop and evaluate focused interventions designed to improve adherence to HIV therapy.
- Evaluate the impact of non-HIV therapies and concomitant diseases, including substance abuse and mental disorders, on women’s eligibility for participation in clinical trials, access to health care, and utilization of and adherence to treatment.
- Support research and development of clinical trial designs and statistical methodologies to evaluate clinical efficacy and reasons for success or failure of anti-HIV treatments among women and girls, including timing of treatment initiation, treatment interruptions and treatment cycling, treatment in the presence of other comorbid conditions, treatment during pregnancy, and the utility of surrogate markers.
- Conduct research to optimize diagnosis and treatment of comorbidities 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 life cycle, including during pregnancy.
- Investigate therapeutic interactions of anti-HIV medications with other medications used by women, including interactions of ARTs with therapies for OIs; therapies for illnesses that affect women specifically, disproportionately or differently from men; hormonal treatments; treatments for substance abuse; and complementary and alternative medicine approaches.
- Evaluate the long-term effects of anti-HIV therapy on morbidity and mortality among girls and women across the life cycle.
- Measure quantity and frequency of alcohol and illicit substance use in treatment and ART pharmacology studies.
- Study the role of HPV vaccination in males and females in reducing the risk of HPV-associated cancers among women and girls with HIV.
- Elucidate the effects of ART on the occurrence of HPV-associated cancers in females.
- Conduct studies on the detection, treatment, and prevention of gynecologic disease in HIV-infected women and girls.

OBJECTIVE–F: *Consequences of HIV/AIDS*

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

STRATEGIES

- Conduct multidisciplinary research to understand the synergistic effects of HIV-related disease progression and premorbid and comorbid clinical and psychosocial conditions affecting women and girls, and the mechanisms underlying these effects; develop interventions to enhance physical and mental health outcomes.
- Develop and evaluate interventions that target HIV-serodiscordant couples to prevent transmission 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 reproductive decisionmaking. This includes research on the decision to disclose HIV status and the consequences of disclosure.
- Support research to improve understanding of reproduction intentions and sexual behaviors of women who are or whose partners are HIV-infected, and how fertility intentions are influenced by highly active antiretroviral therapy (HAART); develop and evaluate accessible assisted reproductive technologies designed to assist in meeting goals for reproduction without vertical or horizontal HIV transmission.
- Conduct research to examine the consequences of HIV infection and treatment on women's and girls' access to, receipt of, and adherence to treatment for comorbid conditions, including other infectious and noninfectious diseases, substance abuse, and psychiatric illness.
- Examine the association between gender-specific physical and psychosocial consequences of HIV disease and HIV-related treatment initiation and maintenance.
- Develop and evaluate interventions to reduce adverse psychological, social, and economic consequences for women and girls infected or affected by HIV/AIDS, such as educational and economic opportunities, access to treatment and care, and prevention of 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—G: Access to Research and Services

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 HIV risk behaviors, HIV transmission, and access to appropriate HIV care, support, treatment, and prevention services.
- Support research to develop effective strategies for the linkage, coordination, and integration of HIV care, support, treatment, and prevention services with primary medical care; drug, alcohol, and mental health treatment; STI services; cancer care, particularly cancer screening programs; reproductive health and family planning services; educational services; and community social services.
- Conduct research to examine transition of HIV/AIDS care across the lifespan, from pediatric to adolescent to adult care, and from adult to geriatric care, and develop interventions to optimize transition of care.
- Support research to understand the impact of policy and policy change—such as health care, health sector reform, health care financing systems, legislation, and regulations—on the delivery and utilization of HIV-related services, HIV risk behavior and transmission, and HIV/AIDS disease outcomes among women and girls.
- Encourage multidisciplinary research to identify unmet needs and elucidate barriers for women and girls to achieving optimal HIV care, support, treatment, and prevention services.
- Support research to study and address factors that influence the full participation of women and girls in HIV/AIDS-related research, including clinical trials for novel therapeutics and vaccines.
- Support research on effective strategies for disseminating products, findings, and information from HIV/AIDS-related research to women, girls, their communities, and policymakers.

OBJECTIVE–H: *Ethical Issues*

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 women and girls who are 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.
- Investigate the unintended consequences of policies and practices (including research practices) that provide special benefits to HIV-infected—as compared to uninfected and unaffected—women and girls (e.g., preferential treatment, health care benefits, access to medications, and social services). Conduct research to examine and determine the contexts and factors that influence when the consent process is fully voluntary and is an informed aspect of the consent process.
- Investigate unintended harms and benefits that may accrue to women and girls, their families, and their communities as a result of participation in research studies.
- Examine the ethical risks and benefits of studies that involve treatment versus observation of women and girls.
- Investigate the ethical impact within a community of studies in which clinical trials provide the only access to therapeutics for women and girls.
- Assess potential negative and beneficial 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 breastfeeding and its alternatives.
- Study the ethical issues related to participation of women and girls in clinical trials.

Racial and Ethnic Populations

AREA OF EMPHASIS

Racial and Ethnic Populations

SCIENTIFIC OBJECTIVES AND STRATEGIES**OBJECTIVE—A: *Determinants of Risk***

Develop and conduct population-specific primary research that focuses upon the individual, interpersonal, organizational, cultural, and community determinants of risk.

STRATEGIES

- Examine the impact of traumatic stressors upon HIV-risk behavior and HIV resiliency in indigenous domestic populations. These populations include Native Americans, Alaska Natives, Native Hawaiians, and Pacific Islanders.
- Develop studies that assess the impact of acculturative stress and historical trauma upon HIV-risk behaviors and HIV-health-seeking behavior among those disproportionately affected by the epidemic of HIV infection, including racial and ethnic populations.
- Explore the effect of poverty, residential segregation, educational opportunity disparities, incarceration, and health illiteracy upon the ongoing disparity in HIV transmission among racial and ethnic populations across the lifespan.
- Increase the emphasis on research that examines the influence of race, ethnicity, language fluency, and gender, independently and collectively, upon the social and cultural contexts of HIV acquisition, transmission, and risk.
- Stimulate research to identify what constitutes sexual behavior ‘norms’ in racial and ethnic populations.
- Determine the impact of gender-based violence, intimate partner violence, and a history of childhood sexual abuse upon HIV risk in racial and ethnic minority populations, including transgenders.
- Promote primary research on the determinants of HIV risk, including substance abuse, in racial and ethnic minority transgendered individuals, social networks, and underlying health disparities.
- Stimulate research on the impact of social and sexual networks upon HIV resiliency and risk.

- Design and conduct studies that determine the impact of stigma, racism, and racial/cultural stereotyping in promoting or impeding early and sustained access to HIV prevention, care, and treatment.
- Stimulate research that explores the influence of bias, racial and cultural prejudice, and homophobia upon health care providers, health care systems, and HIV-testing behaviors among the racial and ethnic populations they serve.
- Explore the effects of hormonal replacement and its biological impact upon racial and ethnic minority transgenders and HIV risk.
- Study the biological (including genetic), environmental, and physiological factors that affect HIV acquisition, transmission, and progression within racial and ethnic populations.
- Explore the behavioral, biological, cultural, and social factors that affect HIV risk, acquisition, and transmission in older women, especially women of color.
- Stimulate exploratory research upon the impact of migration upon HIV-risk behavior, comorbid sexually transmitted infections, and disease burden within racial and ethnic populations.
- Recruit and retain racial and ethnic minorities in numbers sufficient to provide adequate statistical power to detect racial and gender differences in NIH-sponsored studies, especially Phase III clinical trials.
- Explore the impact of adolescent and youth culture upon adolescent HIV-risk behaviors, especially among racial and ethnic populations, to determine how this affects them, their social peer networks, and their risk of HIV acquisition.
- Study the social networks of youth of color and the impact the age of a partner has upon their HIV risk and the risks to those within their respective sexual networks.

OBJECTIVE–B: *Intervention Research*

Develop population-specific, theory-based interventions that focus upon individual risk, community norms, organizational and sociocultural factors, as well as biological susceptibility.

STRATEGIES

- Identify effective interventions for racial and ethnic minority communities, as well as for those in sexual minority within those communities, that prevent HIV acquisition and transmission.
- Recruit and retain racial and ethnic minorities in numbers sufficient to provide adequate statistical power to detect racial and gender differences in NIH-sponsored studies.
- Explore processes of engagement that make for effective community prevention responses.
- Study the social aspect of prevention delivery from the role of key informants to key community organizations, and the linkages necessary for community acceptance of prevention.
- Identify the factors that reliably predict and assess the level of community readiness to engage with HIV prevention or other research interventions.
- Fund community-academic partnerships that have demonstrated linkages with community-based organizations to promote the development of effective and accepted community prevention interventions.
- Develop, pilot, and test new models of HIV behavioral interventions that incorporate common stressors and experiences for racial and ethnic minorities, including acculturation, racism, and stigmatization.
- Identify structural and behavioral factors that affect HIV testing and testing frequency among racial and ethnic populations.
- Determine what venues are perceived as acceptable and accessible for HIV testing by racial and ethnic populations.
- Encourage the development, piloting, and testing of prevention efforts for high-risk uninfected individuals within health care systems for non-HIV-related conditions.
- Identify successful interventions to increase access to and quality of care in racial and ethnic communities, and their subsequent impact upon HIV transmission in these communities.
- Develop interventions that document the impact of evidence-based quality of care and best practices upon HIV disease outcome in racial and ethnic populations.

- Explore social marketing and health communication strategies used by the private sector to develop new effective HIV prevention interventions in racial and ethnic minority populations.
- Identify effective, efficient, and sustainable HIV prevention interventions for rural communities, especially those with undocumented immigrants.
- Develop, pilot, and test HIV prevention interventions for efficient and rapid translation into the field.
- Develop, pilot, and test new models of HIV behavioral interventions that incorporate common resilience factors for racial and ethnic populations, including cultural identity, spirituality, and collectivism.

OBJECTIVE–C: Methodology

Develop and test innovative methods and measures to accurately assess determinants of risk, including resiliency and social norms in populations at highest risk for HIV infection.

STRATEGIES

- Develop, pilot, test, and evaluate new measures of HIV-risk behavior that are culturally and contextually appropriate for racial, ethnic, and sexual minority populations.
- Develop and test new sampling methodologies for populations most heavily affected by HIV infection.
- Develop and standardize assessment tools that are designed for the at-risk community in which they are to be used, including rural populations, foreign-born individuals, and racial and ethnic populations.
- Develop novel sampling methods to enhance the proportion of underrepresented populations that continue to be disproportionately affected by HIV infection in clinical and prevention research, such as racial and ethnic minorities, adolescents, the homeless, and indigenous populations.
- Emphasize the development of intervention evaluation methods that can translate results quickly from the field to the communities affected.
- Evaluate models for HIV prevention, care, and treatment with HIV-infected individuals in heavily affected communities utilizing comprehensive, culturally and contextually appropriate interventions.
- Develop, pilot, and test effective models for increasing the awareness of the benefits of HIV testing in racial and ethnic minority populations.
- Develop models to include community-initiated HIV prevention interventions and evaluation in community-academic partnerships, especially in disproportionately affected communities.
- Incorporate community-based participatory research principles into all community-based projects to ensure the bidirectional benefit and investment of the community and the research team.
- Identify the components of effective outreach, and develop models of successful outreach with quantification of that success.
- Identify factors that increase HIV risk among racial and ethnic minority transgendered individuals; develop, pilot, and test models of HIV prevention that modify those risks.

OBJECTIVE–D: *Factors Affecting Risk*

Support high-risk, high-impact research that explores the unique factors that affect HIV-risk behavior, acquisition, transmission, and resistance for those at highest risk for HIV infection within racial and ethnic minority communities.

STRATEGIES

- Explore the interface between countries, their borders, and the impact of these borders on HIV-risk behavior within the racial and ethnic populations along those borders.
- Stimulate public-private-academic collaborations that study the unique factors that affect HIV-risk behavior in racial and ethnic populations and develop interventions based upon these unique factors.
- Identify the impact of the provision of stable housing upon HIV-risk behavior, disease outcome, and treatment adherence.
- Determine the impact of insurance payor status on care-seeking behavior, treatment adherence, and remaining in care.
- Explore the relationship between employment type (e.g., day labor versus part-time) upon HIV-risk behavior in heavily affected communities, including racial and ethnic populations.
- Stimulate multidisciplinary research that links risk management (e.g., substance abuse treatment) and HIV-risk reduction through novel cross-DHHS (U.S. Department of Health and Human Services) agency partnerships and joint funding.
- Determine the impact of educational initiatives upon health literacy and the downstream impact upon HIV-risk awareness and behavior.
- Fund collaborative, multidisciplinary partnerships that target core sociocultural factors in HIV transmission and explore the impact upon HIV-risk behavior and transmission.

Research in International Settings

AREA OF EMPHASIS

Research in International Settings

SCIENTIFIC OBJECTIVES AND STRATEGIES**OBJECTIVE—A: Capacity Building**

Develop a sustainable, collaborative research environment by utilizing and enhancing in-country capacity.

(The scientific objectives of A and B are of equal weight and serve as a prerequisite foundation for objectives C through I.)

STRATEGIES**Site Development**

- Encourage the integration of NIH-supported research programs being conducted in resource-limited countries by U.S. researchers with established in-country programs, including collaboration with local investigators on strategic planning for research.
- Assess existing sites and, as needed, further develop sustainable, existing in-country sites, or establish new international research sites as rapidly as possible to address urgent and emerging scientific opportunities.
- Enhance capacity for the conduct of basic and applied prevention and treatment research, with emphasis on maintaining and developing both Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) requirements for large-scale clinical trials, through:
 - ▶ strengthening laboratory capacity through the provision of required equipment and human resource development, with appropriate quality assurance and training;
 - ▶ developing clinical capabilities through research training and “hands-on” research experiences;
 - ▶ developing affordable alternatives to viral load and CD4+ cell counts and expensive laboratory monitoring for treatment efficacy and toxicity;
 - ▶ supporting the analysis of scientific and research-based international databases and developing common laboratory information management systems;
 - ▶ enhancing data collection and analysis capabilities;
 - ▶ addressing barriers in maintaining, optimizing the use of, and ensuring human subject protections related to repositories of biological samples in resource-constrained countries;

- ▶ developing and testing strategies for recruitment and retention of participants in prevention, treatment, and care studies;
 - ▶ enhancing the ability to ensure protection for human subjects involved in research and the ethical conduct of research, including informed consent and issues specific to women and children and vulnerable populations, including injection drug users (IDUs), men who have sex with men (MSM), prisoners, and sex workers;
 - ▶ enhancing mechanisms for information exchange among investigators, including enhanced electronic communication;
 - ▶ conducting research on rapid and sustainable scale-up from pilot projects and/or early Phase I and II trials to large research studies, including Phase III trials, and on how to apply and implement research findings to the general population;
 - ▶ strengthening community advisory boards to participate in the development and design of clinical trials and other research, as well as in the translation of research results into programs and policies;
 - ▶ strengthening financial management, accounting, and business office practices; and
 - ▶ strengthening library services and access to scientific resources.
- Build global capacity to conduct operational research, including outcome and cost-effectiveness studies and modeling, to rapidly address emerging priorities in prevention, treatment, and care.
 - Conduct studies on incidence and feasibility, using appropriate incidence measures (e.g., population-specific assays), in order to identify sites suitable for the conduct of efficacy trials of HIV prevention, treatment, and care interventions.
 - Develop and provide training at international sites conducting vaccine studies on the role and responsibilities of an institutional biosafety committee (IBC).
 - Develop regional approaches to research (e.g., through regional meetings and training) to enhance communication and to address common issues and needs among countries in a region.

Collaboration and Coordination

- Ensure that foreign investigators are full and equal partners with U.S. scientists in the design, conduct, and analyses of clinical studies.
- Enhance coordination of NIH international AIDS research, particularly when multiple projects are active in the same country and/or region.
- Encourage the continued development of research collaborations between international and U.S. investigators, ensuring project relevance to strategic planning at the local level, to maximize the

research effort in resource-limited settings; and encourage U.S. researchers to participate at the developing country research site to better understand the challenges of conducting research and providing care and services in such settings.

- Provide assistance to foreign collaborators in addressing regulatory issues and special oversight mechanisms.
- Coordinate with other U.S. Government agencies, including the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), the Department of Defense (DoD), the Health Resources and Services Administration (HRSA), and the State Department (e.g., the Office of the Global AIDS Coordinator [OGAC] and the President's Emergency Plan for AIDS Relief [PEPFAR]).
- Work with foreign governments, international organizations (e.g., the World Health Organization [WHO]), the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM), nongovernmental organizations (NGOs), private industry, foundations, and alliances (e.g., the Global HIV Vaccine Enterprise) to help identify priorities, gain efficiencies, and reduce overlap in the development and testing of vaccines, microbicides, drugs, and other prevention, care, and treatment strategies, including behavioral interventions.
- Explore collaborations with reputable indigenous health providers and nonphysician health research professionals (e.g., nurses, pharmacists, etc.) to better understand their roles and practices in AIDS care and prevention; to facilitate their involvement as partners and indigenous health professionals in global AIDS research, care, and prevention; and to identify practices that may add value in treating and preventing diseases in diverse geographical settings.

Ethical Issues

- Ensure that research projects are designed to benefit the countries in which the research is being conducted.
- Enhance the capability of institutions in resource-limited settings to conduct independent scientific and ethical reviews, while ensuring timeliness of the review process.
- Ensure education/cross-fertilization between resource-limited countries' ethical review committees and U.S. institutional review boards (IRBs), and educate U.S. IRBs about cultural issues in developing countries.
- Ensure the participation of local researchers/scientists, communities, NGOs, governments, indigenous leadership of vulnerable populations, and other stakeholders in the development of research protocols.
- Ensure that ethical challenges in both research and the implementation of research results in resource-limited settings are clearly described and addressed in grant proposals.

- Ensure confidentiality of information about HIV-infected individuals, including information on individuals in treatment for substance abuse.
- Ensure that ethical review mechanisms, such as informed consent forms, are relevant and appropriate to the country where the research is conducted and are placed in cultural context.
- Conduct workshops on ethical principles and their implementation in research, encouraging countries to develop their own set of ethical guidelines and procedures, to include the principles of respect for persons, beneficence, and justice, and the application of informed consent, assessment of risks and benefits, and selection of subjects.
- Encourage in-country scientists and leaders to work closely with local journalists to foster understanding of science, the role of research, and relevant ethical issues.
- Conduct research designed to identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings, including a focus on informed consent.

Technology Transfer and Translation of Research Results

- Ensure results are provided to and understood by participants and staff involved in research studies and available for their use.
- Develop distance learning approaches to enhance communication of research results and translation into prevention, treatment, and care programs.
- Provide improved access to information concerning treatment and prevention guidelines and the results of research through enhanced information technology.
- Facilitate development of locally appropriate and acceptable HIV prevention and treatment guidelines, by including behavioral, basic, epidemiological, and clinical research findings.
- Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptom management, clinical training, and patient care programs once research studies are completed.
- Support operational research based on implementation science and innovative research designs not limited to randomized clinical trials (RCTs).

OBJECTIVE–B: Mentoring and Training Investigators

Develop an in-country community of investigators committed to a culture of leadership in research through providing sustainable mentoring for junior investigators and career development opportunities for new, mid-career, and senior investigators.

(The scientific objectives of A and B are of equal weight and serve as a prerequisite foundation for objectives C through I.)

STRATEGIES

- Ensure the leadership role of in-country investigators and influential individuals in countries where studies take place by involving them in all stages of the research, including conceptualization of the research question, study design, development of protocols, study implementation and collection of data, data analysis, publication and presentation of research results, and interaction with the media and law enforcement officials.
- Provide sustainable career development opportunities for new, mid-career, and senior investigators (e.g., similar to long-term career awards and institutional grants offered domestically) in resource-limited international settings.
- Develop in-country training partnerships, and support “south-to-south” training to enable investigators to obtain training appropriate for the areas in which they will work by (1) developing a cadre of in-country scientific professionals, and (2) providing opportunities to enable trained investigators returning to their home countries to serve as training resources for others.
- Continue to support research training, both in-country and in the United States, of clinicians (physicians and nonphysician professionals, e.g., nurses, midwives, pharmacists, etc.), public health professionals and community health workers, and scientists from developing nations to enhance the conduct of research on HIV, AIDS, sexually transmitted infections (STIs), and other HIV-related coinfections, malignancies, and comorbidities, including research training related to (1) biomedical, social, and behavioral prevention research, (2) prevention of mother-to-child transmission (MTCT), (3) treatment and care, (4) clinical trials of therapeutic strategies, (5) development and testing of vaccine candidates, (6) impact of alcohol and other substance abuse/dependence on HIV transmission, treatment, and disease outcome, (7) reproductive health, including microbicides, and (8) disease progression.
- Provide training in data collection, management, and analysis for in-country research personnel.
- Provide training to enable in-country researchers to meet the requirements of GCP and GLP, including training and maintenance of medical records.
- Provide training in the ethical conduct of research, including informed consent, establishment of community advisory boards, and other topics related to the protection of human subjects.

- Provide training in all aspects of grantsmanship, including preparation of grant proposals, registration for electronic submission, grants management, reporting requirements, research administration, and fiscal accounting.
- Provide training to ensure that clinicians and other health care workers are knowledgeable about infection control principles and can implement proper procedures in resource-constrained countries.
- Enhance training in translational, operational, and health services research.

OBJECTIVE–C: Structural Interventions

Conduct studies to identify effective structural and policy interventions to address the AIDS epidemic.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Determine barriers and facilitators to acceptance of voluntary counseling and testing (VCT), and develop more comprehensive and integrated health system-level approaches to the provision of VCT, including:
 - ▶ assess new VCT approaches for cost-effectiveness and impact on reducing risk from sexual behavior and drug use in settings with varying levels of HIV seroprevalence;
 - ▶ integrate VCT into other existing health services, including family planning; and
 - ▶ change community norms for seeking VCT that encourage knowledge of one’s status, help mitigate social harm, and reduce HIV stigma.
- Identify the most effective and sustainable ways for schools, leisure locations, and worksites to support behavior change interventions.
- Investigate the effectiveness of community-based and community-level HIV prevention programs, including prevention education and strategies to evaluate, replicate, and extend effective behavioral interventions.
- Investigate the structural and policy-related human rights limitations that affect HIV prevention, treatment, and care for vulnerable populations (e.g., MSM, prisoners, IDUs, and sex workers), including laws and policies related to discrimination against minorities engaged in same-sex behavior between consenting adults, and evaluate the effectiveness of rights-based interventions to improve HIV disease outcomes.
- Ensure that all research is conducted in culturally appropriate content, form, and format.
- Ensure that all research is conducted in accordance with international standards of human rights principles and in accord with the dignity of persons.
- Evaluate the effectiveness of expanded access to drug abuse and treatment programs, including sterile injection equipment and syringe exchange programs, and the policy-level changes necessary to implement such expanded interventions.
- Develop and test strategies for encouraging voluntary partner notification within the context of families and couples counseling.
- Evaluate the effectiveness of expanded access to male circumcision programs and the policy-level changes necessary to implement such expanded interventions.

OBJECTIVE–D: Interventions to Alleviate Stigma and Discrimination

Support AIDS research to develop interventions that address the issues of sex/gender, age, power relationships, stigma, and discrimination.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Conduct research on sex/gender and age differences and/or inequities in access to and use of resources, information, and prevention and care services, as well as adherence issues.
- Conduct research on the impact of new technologies and structural interventions (e.g., male circumcision) on gender and power relationships.
- Encourage analysis of sex/gender and age differences in all relevant HIV-related research.
- Study gender-related social and behavioral factors affecting acquisition of HIV infection, including intimate partner violence and the conflicting demands of childbearing and avoidance of disease.
- Study gender-related biological factors affecting susceptibility to HIV infection, including the use of contraception and the presence of sex-specific conditions, such as human papillomavirus (HPV) infection and cervical cancer.
- Study age-related social, behavioral, and biological factors (including the use of medications) affecting susceptibility to HIV infection and its transmission.
- Study the psychological impact of HIV infection in women, including their role as heads of households and/or caregivers, the impact of additional pregnancies, and family support.
- Develop interventions to mitigate the negative social consequences of HIV infection related to AIDS stigma and discrimination, with particular emphasis on children infected with or affected by HIV (e.g., AIDS orphans).
- Evaluate laws and legal policies at the local, State, and national levels that operate to sustain stigma.
- Design and evaluate strategies to reduce stigma and discrimination and increase willingness of individuals to enter into voluntary counseling and testing; identify, accept, and implement alternative infant feeding practices; and receive and adhere to antiretroviral therapy (ART) and antituberculosis drug regimens.
- Support training of community and public health leaders to become role models in the implementation of such strategies and interventions.

OBJECTIVE–E: Prevention of Risk Behaviors in Social Settings and Networks

Study the significance of interactions among individuals in groups engaging in various risk behaviors, and develop and evaluate interventions and strategies to prevent HIV-risk behaviors in social settings and high-risk networks.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Develop sustainable behavioral and community-specific interventions to address multiple risk factors.
- Conduct research to integrate the multiple components of diverse issues of sexuality, alcohol and other substance use, and mental health into HIV prevention programs.
- Develop and test prevention strategies that address relationships between noninjection drug use and sexual transmission.
- Develop interventions targeted to both HIV-infected and HIV-uninfected individuals that are designed to appeal to specific populations such as women, men, adolescents, and the military.
- Develop and test prevention interventions to be used in the family context to prevent risky behavior and HIV acquisition and transmission by its members.
- Study the role of migration in the spread of the HIV epidemic in diverse geographical regions.
- Identify the most effective means to reach and prevent HIV transmission among mobile populations, including migrants, refugees, and those displaced by national conflict or natural disaster.
- Support cross-border studies to study virus transmission issues as well as the impact of various policies and structural interventions related to migration and immigration.
- Conduct studies to develop interventions at multiple levels (e.g., individual, couple, group, and society) that reflect and address regional aspects of the epidemic.
- Investigate the role of mental health conditions (e.g., depression) and alcohol and other commonly used psychoactive substances in promoting or facilitating high-risk sexual behaviors that reduce the efficacy of prevention strategies.
- Define sexual and drug use behaviors and their predictors in HIV-infected populations, and design and test interventions to reduce the risk of HIV transmission.
- Determine the factors involved in high-risk social networks (e.g., injection and noninjection drug users and heavy drinkers and/or alcohol-dependent individuals) that influence the rates and patterns of HIV infection, and design prevention programs based on these results.

- Encourage molecular epidemiology studies of viral diversity in the context of social networks.
- Study how alcohol use, including systems of payment using alcohol, affects increases in HIV risk in seasonal and nonseasonal migrant populations.
- Conduct studies to identify sustainable interventions at the levels of the individual, social network, community, and society to prevent HIV and hepatitis C virus (HCV) transmission as a result of high-risk sexual activity and/or drug use practices.
- Devise strategies to prevent initiation of drug use, alcohol dependence, and transition to riskier drug practices, such as initiating drug injection and sharing of injection equipment.

OBJECTIVE–F: Biomedical Prevention Interventions

Develop and evaluate biomedical prevention interventions and strategies.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Evaluate techniques for detection of acute HIV infection, and study the effects of early identification of potential HIV transmitters on HIV infection spread in different settings.
- Utilize population-based studies to examine basic scientific questions about HIV infection, mechanisms of transmission, and host responses, including viral evolution, viral diversity, human immunology, and mucosal factors in transmission.
- Study the risk of transmission of drug-resistant strains of HIV.
- Develop and evaluate methods for increasing access to, acceptability of, and adherence to biomedical interventions.
- Study and integrate the behavioral aspects of biomedical interventions and strategies.

Male Circumcision

- Determine the durability of effectiveness of circumcision in reducing HIV transmission risk in men.
- Study the effect of male circumcision on HIV transmission risk from men to women and from men to men.
- Develop and evaluate innovative strategies for the safe and effective delivery of male circumcision and other male-oriented prevention services to prevent or reduce HIV transmission.
- Determine the factors affecting male circumcision use and acceptance.
- Study the sociocultural aspects that may inhibit or encourage use of circumcision.
- Study the technical training and implementation requirements for widespread uptake of circumcision interventions.
- Determine the cost-effectiveness of male circumcision in limiting transmission and curtailing the expansion of the epidemic.

Antiretroviral Use

- Determine the effectiveness of pre- and postexposure antiretroviral (ARV) prophylaxis in prevention of sexual and blood-borne HIV transmission.
- Determine the most effective ARV agents or combinations of agents to reduce transmission risk.
- If proven effective, determine the social, cultural, and practical factors affecting ARV use and/or providing barriers to implementation of exposure prophylaxis.

Vaccine Development

- Continue the accelerated efforts toward development of vaccine candidates suitable for use around the world, and foster the development of vaccines to optimize characteristics appropriate for broad international use, including candidates exhibiting low cost with ease of production and administration, as well as stability.
- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects.
- Provide a scientific knowledge base (incidence, viral subtypes, major histocompatibility [MHC] types, and natural history) to guide decisionmaking regarding the need for clinical trials in international sites and to conduct trials in these sites and communities according to the highest clinical and ethical standards.
- Identify suitable populations of adults and children to enroll in clinical trials of candidate vaccines, while ensuring equitable and appropriately representative gender balance in enrollment.
- Conduct Phase I, Phase II, and Phase III clinical trials for safety, immunogenicity, and efficacy, with appropriate surrogate markers and measures of correlates of protection with suitable candidate vaccines in domestic and international settings.
- Enlist the participation of local community representatives in the development of appropriate trial protocols, as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively address the social and medical concerns of the participants; and establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale of the study.
- Examine relevant behavioral issues related to the conduct of vaccine research and its acceptability in diverse populations.
- Conduct research on the social and economic impact of vaccines and their cost-effectiveness.

Microbicides and Barrier Methods

- Discover and develop candidate microbicides and other physical/chemical barrier methods to prevent sexual HIV transmission.
- Conduct Phase I, Phase II, and Phase III clinical trials for safety and efficacy with suitable candidate microbicides in domestic and international settings.
- Develop appropriate biological and surrogate markers of safety or protection.
- Determine the efficacy and use of prevention interventions, including microbicides and other physical/chemical barrier methods, and determine the factors affecting their use and acceptance.
- Study the sociocultural aspects that may inhibit or encourage microbicide use and barriers to adherence.
- Study the sociocultural and behavioral concerns related to partner involvement and acceptance of microbicide use or covert use in the absence of partner willingness or acceptance.
- If found to be effective in preventing HIV transmission/acquisition, determine the cost-effectiveness of microbicides and other physical/chemical barrier methods in limiting transmission and curtailing the expansion of the epidemic.

STIs and Other Diseases

- Determine the efficacy and cost-effectiveness of syndromic management of STIs among HIV-infected individuals to prevent HIV transmission.
- Improve clinical management of viral STIs in HIV-infected individuals, emphasizing coinfections with herpes simplex virus (HSV)-2 and HPV.
- Identify gender-related biological factors affecting susceptibility to HIV infection, including the use of hormonal contraceptives and the presence of gender-specific conditions such as HPV infection, cervical cancer, and genital ulcer disease.
- Examine the impact of coinfection with other endemic diseases on HIV disease, including the risk of acquiring and/or transmitting HIV infection and disease progression.
- Determine the role of sexual transmission of HCV in coinfection with HIV.

Substance Abuse

- Develop and evaluate innovative, culturally relevant, contextually appropriate alcohol and drug abuse treatment programs for their utility as HIV and HCV prevention approaches in different international settings.
- Develop and evaluate approaches for drug and alcohol abuse programs among HIV- and HCV-coinfected patients to improve adherence with drug/alcohol treatment strategies.
- Develop and evaluate innovative strategies for identifying “hidden populations” of young, older, and out-of-treatment drug users.

MTCT: Considerations for the Mother, Child, and Family

- Develop and evaluate strategies for primary prevention, i.e., prevention of HIV acquisition by adolescent girls and women.
- Investigate methods to improve reproductive health in serodiscordant couples, including HIV-risk reduction in *in vitro* fertilization.
- Develop and evaluate strategies for prevention of unwanted pregnancy by HIV-infected adolescent girls and women.
- Investigate the mechanisms of and risk factors for *in utero*, intrapartum, and postnatal MTCT by HIV-infected adolescent girls and women.
- Investigate the unique immune status of pregnant women and their infants and develop immune interventions to interrupt HIV transmission.
- Facilitate and develop targeted prophylactic drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Further evaluate and adapt known efficacious interventions in infants, mothers, or both to prevent MTCT (antiretroviral prophylaxis, cesarean section before labor and before ruptured membranes, complete avoidance of breastfeeding, exclusive breastfeeding).
- Develop effective, safe, and feasible strategies for prevention of MTCT of HIV, using interventions that are affordable and can be implemented in resource-constrained settings, especially with regard to prevention of MTCT through breast milk.
- Study factors associated with unwanted repeat pregnancies in HIV-infected women.
- Evaluate strategies to reduce the morbidity and mortality associated with MTCT of HIV, including:
 - ▶ the role of maternal and infant nutrition during the peripartum and postpartum periods;

- ▶ the impact of the health status of HIV-infected mothers on the survivability of both HIV-infected and HIV-uninfected children; and
- ▶ short- and long-term toxicity of ARVs used for prevention of MTCT in women during pregnancy and in their offspring who were perinatally exposed.
- Evaluate and reduce the maternal and pediatric morbidity associated with mode of delivery.
- Develop strategies to reduce the risk of postpartum morbidity (e.g., endometritis, hemorrhage, pneumonia) related to cesarean section for prevention of MTCT of HIV.
- Develop strategies to reduce the risk of iatrogenic preterm birth and associated respiratory morbidity.
- Evaluate mechanisms to reduce the maternal and pediatric morbidity and mortality associated with infant feeding modality, including the role of exclusive breastfeeding and acceptability of safe breastfeeding alternatives.
- Evaluate the development of antiretroviral resistance, clinical outcomes among HIV-infected women and their children, and impact on subsequent pregnancies according to receipt of/ exposure to antiretrovirals (*in utero*, intrapartum, and postpartum/postnatal).
- Quantify more precisely the risk of MTCT when maternal HIV infection is acquired during pregnancy, including:
 - ▶ the effectiveness of known efficacious interventions to prevent MTCT; and
 - ▶ development of strategies for detecting or reducing maternal incident infection during pregnancy.
- Evaluate strategies and identify the obstacles and facilitators for scaling up successful interventions for prevention of MTCT of HIV.

OBJECTIVE—G: Treatment Research

Develop and evaluate the most effective, setting-specific strategies for care and treatment of HIV and HIV-related conditions and their sequelae among HIV-infected and HIV-affected children, adolescents, and adults at all stages of the life course.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Determine affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment.
- Evaluate and monitor treatment efficacy, adherence, side effects, drug-drug interactions, and toxicity of ARVs and prophylaxis medications against major coinfections in pediatric, adolescent, and adult (including over age 50) populations in resource-constrained settings.
- Collaborate with clinicians from resource-limited countries to recruit and retain acute and early HIV infection cases in treatment research programs.
- Determine the role of pharmacogenetics/pharmacokinetics and identify appropriate ARVs that can be used in specific populations (e.g., children, adolescents, and adults at all life stages) in resource-constrained countries.
- Determine the efficacy of ARV regimens on various clades prevalent around the world.
- Investigate interactions of ARVs with alcohol, drugs of abuse, or medications used for the treatment of substance abuse.
- Develop, evaluate, and implement programs to prevent discrimination in the provision of ARV treatment.
- Characterize the clinical course of HIV infection in diverse geographic settings.
- Identify conditions that emerge as a consequence of ART and longer survival, such as malignancies, neurological and neuropsychological conditions, and metabolic and nutritional dysfunctions.
- Support the long-term followup of children exposed to ART *in utero* and/or postpartum to evaluate possible late effects of ARV exposure.
- Assess the impact of nutritional status and nutritional interventions on patient survival and the efficacy and tolerability of ART, including measuring the rate of immune system deterioration.
- Develop and evaluate public health models, such as family and community models of care for infants to older adults that integrate HIV/AIDS care and other existing health services in a single setting to maximize outcomes and avoid duplication of effort.

- Enhance interdependent programs such as programs for tuberculosis (TB) control and management of other comorbid conditions, alcohol and other substance abuse/dependence treatment programs, maternal and child health services, and support services for the elderly.
- Develop and evaluate strategies to initiate and provide care to targeted groups of individuals such as health care workers, security forces, and teachers.
- Conduct community-based studies that assess the impact of community mobilization on treatment success.
- Examine the effectiveness of a variety of approaches to the administration of therapy (e.g., directly observed therapy or directly delivered therapy).
- Conduct studies, including clinical trials and operational research, on the quality of treatment, its effectiveness, and its efficacy.
- Develop and test strategies, including promotion of treatment literacy, to support adherence in adults of all ages, adolescents, and children to medication regimens to enhance therapeutic outcomes and limit the development of drug resistance.
- Investigate the impact of alcohol abuse, drug abuse, and other associated comorbid conditions on HIV disease progression, adherence to treatment regimens, and clinical outcomes.
- Conduct research on biological, behavioral, and psychosocial effects related to the natural history and care of HIV disease among children and adolescents.
- Develop and evaluate suitable and sustainable approaches to the diagnosis of HIV infection, especially for children under the age of 18 months.
- Develop and evaluate suitable and sustainable approaches to monitoring the effectiveness and safety of HIV treatment, especially with regard to affordable technologies to measure CD4+ cell counts and viral load (or appropriate alternatives).
- Assess the cost-effectiveness of ARVs in resource-limited settings and determine the minimal level and methods of targeted drug resistance monitoring necessary in those failing therapy and in pregnant women.

OBJECTIVE–H: *Endemic Diseases and HIV*

Study the interactions between HIV infection, comorbidities, and endemic diseases, with a particular focus on endemic diseases that affect HIV care and are a part of the spectrum of HIV comorbidities, and develop strategies to optimize their integrated prevention, diagnosis, treatment, and care.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Examine the role of coinfection and other endemic diseases and their treatment in modulating HIV infection or disease, including risk of acquiring and/or transmitting HIV infection, disease progression, and the use of ART.
- Determine the impact of ART on susceptibility to infection with endemic diseases, and on their natural history.
- Determine the impact of ART on the efficacy of treatment and prophylaxis for other endemic diseases.
- Investigate drug-drug interactions of ARVs and drugs used to prevent and treat endemic infections and/or other manifestations of such endemic infections.
- Define the spectrum, incidence, and risk factors for HIV-related sequelae (e.g., coinfections such as TB, HCV, and HPV, malignancies, and organ system-specific manifestations such as renal disease, eye disease, and urologic, neurological, and neuropsychiatric conditions) in adult, adolescent, and pediatric populations specific to individual regions in diverse geographic settings.
- Determine optimal ways of integrating treatment for HIV disease with prevention of and treatment for opportunistic infections (OIs), endemic diseases, and comorbidities, especially TB, including clinical research to assess clinical outcome and operational research to determine cost-effectiveness.
- Develop, study, and widely and uniformly deploy new, low-cost, and rapid diagnostic and drug susceptibility tests for comorbid and endemic diseases (including TB) and new agents and therapeutic strategies to treat drug-sensitive and drug-resistant TB (including multi-drug-resistant [MDR]-TB and extensively drug-resistant [XDR]-TB).
- Develop and study strategies for primary and secondary TB prevention, including prophylactic regimens.
- Develop and study feasible and effective strategies for prevention of transmission of drug-susceptible and -resistant TB in community and health care settings.

- Assess the impact of available antibiotic treatment and prophylaxis regimens to optimize therapeutic approaches for TB and other endemic coinfections in the context of ART, including new therapies for TB and new approaches to administering drugs.
- Determine the safest and most efficient treatment modalities for endemic diseases (e.g., TB, HCV, HIV-associated cancers, and malaria) in the adult, pediatric, and adolescent populations infected with HIV.
- Assess the burden of TB and the relative importance of reactivation versus *de novo* infection in HIV-coinfected individuals in various settings.
- Develop methods to monitor development of antimicrobial resistance by HIV-related and endemic pathogens infecting both study participants and the general population.
- Investigate behavioral and cultural factors related to endemic coinfections, within the context of HIV disease, and develop strategies to enhance and monitor adherence to therapy and prophylaxis for endemic coinfections in HIV-infected individuals.
- Investigate sustainable strategies for preventing, treating, and monitoring response to treatment of endemic diseases in HIV-infected adults, adolescents, children, and infants in resource-constrained settings.
- Determine the safety and effectiveness of available immunizations for endemic pathogens in diverse HIV-infected populations.
- Develop simple clinical algorithms for guiding initiation of prevention or treatment of HIV-related OIs and comorbidities.
- Identify affordable strategies to target high-risk patients for initiation of prophylaxis for HIV-related OIs and comorbidities.
- Conduct studies to better understand the role and mechanism of reinfection and/or superinfection with HCV in coinfecting individuals.

OBJECTIVE–I: *Impact of Prevention and Treatment*

Evaluate the impact of prevention and treatment programs on the HIV epidemic, integrating comprehensive prevention and clinical care in existing health service delivery programs related to HIV/AIDS, while leveraging clinical trial sites for prevention interventions.

(The scientific objectives of C through I are of equal weight.)

STRATEGIES

- Assess the social, psychological, societal, and economic impact of ART on risk behaviors, HIV transmission, and prevalence, including associated behavior change, in individuals (including children), families, and various communities.
- Determine the impact of ART availability on utilization of VCT in various communities.
- Determine the impact of ART availability on entry into care and treatment.
- Determine whether expanded ART care and treatment leads to a decrease in HIV-associated stigma and discrimination.
- Determine effective strategies for integrating the delivery of HIV care with drug treatment, alcohol treatment, TB treatment, and other medical and social services commonly needed by HIV-infected individuals.
- Evaluate the impact of interactions between HIV therapeutics, alcohol, drug abuse, or medications used for the treatment of substance abuse on the maintenance of anti-addiction therapy and on MTCT.
- Determine the impact of ART on breastfeeding behaviors.
- Identify morbidities in HIV-exposed, uninfected infants and young children, using appropriate control populations, in resource-constrained settings.
- Study the direct effects of ART on HIV transmission, e.g., by evaluating the effectiveness of specific ART strategies in curtailing HIV transmission in HIV-serodiscordant couples.
- Determine the public health impact of ART, specifically the likelihood of transmission of drug-resistant virus and the natural history of disease in people infected with a drug-resistant HIV strain.
- Examine the potential use of HIV therapeutic vaccines.
- Determine the impact of ART on the development of drug-resistant strains of HIV in diverse geographical settings, and develop strategies to limit its development. Develop biomarkers that can serve as surrogates for measurement of HIV-risk behavior and can be used to predict and monitor rapid escalation of HIV subepidemics.

- Integrate operational and health services research with clinical research to facilitate the translation of research findings to clinical practice and public health programs and to provide information to inform the scale-up of HIV prevention, care, and treatment programs.
 - ▶ Develop strategies to ensure that prevention efforts in resource-limited countries are simultaneously preserved and enhanced when treatment clinical trials and, later, ART treatment programs are established, and when prevention trials are completed.
 - ▶ Conduct research on how best to deliver prevention education in the care and treatment setting, targeting interventions to both HIV-uninfected and -infected individuals.
 - ▶ Develop culturally appropriate mechanisms to identify persons for whom treatment is indicated and to overcome factors such as stigma and discrimination, which can forestall testing and limit the provision of treatment and care.
 - ▶ Develop links with other agencies and organizations to integrate research with service programs and to develop multidisciplinary prevention research in multiple settings, including medical treatment and community support and care organizations.
 - ▶ Develop strategies to control the HIV epidemic that address multiple health outcomes simultaneously without compromising existing public health infrastructure, while at the same time strengthening infrastructure to improve health outcomes.
 - ▶ Evaluate the impact of scale-up of HIV prevention, care, and treatment programs on the health system as a whole and its ability to deliver other public health services, particularly in resource-limited settings.

