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

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

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 microbicidal 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

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

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

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-naive 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

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 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-positive, 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

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

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

Develop and test innovative research models, methods, and measures to accurately assess risk and protective behaviors in diverse populations, including minority communities.

STRATEGIES

- Develop, pilot, test, and evaluate new measures of HIV risk behavior that are culturally and contextually appropriate for racial and ethnic minorities.
- Develop new models of HIV behavioral interventions that incorporate common stressors and experiences for racial and ethnic minorities, including racism, acculturation, and stigmatization.
- Identify effective interventions for racial and ethnic minority communities to prevent HIV acquisition and transmission, as well as for the sexual minorities within these communities, given the paucity of research in this area.
- Emphasize the development of intervention evaluation methods that can translate results quickly from the field to the communities affected.
- Fund through specific announcements the development and testing of new sampling methodologies in those communities most heavily affected by HIV infection.
- Develop novel sampling methods to enhance the representation of underrepresented populations in clinical and prevention research, such as racial and ethnic minorities, the homeless, and rural individuals, with attention to sampling adequately from indigenous populations.
- Fund the development and standardization of assessment tools that are designed for the at-risk community in which they are to be used, including diverse groups such as rural populations, racial and ethnic minorities, and immigrants.
- Encourage studies to examine the impact of traumatic stressors upon indigenous domestic populations, in numbers that reflect their risk trajectory. These populations include Native Americans, Alaska Natives, Native Hawaiians, and Pacific Islanders. Studies should assess the impact of acculturative stress and historical trauma upon HIV risk behaviors and HIV health-care-seeking behavior.

OBJECTIVE–B

Examine the social, cultural, and structural determinants; social structures; social environments; and health care systems that sustain, perpetuate, resist, or counter health disparities among racial and ethnic minorities.

STRATEGIES

- Explore the effect of poverty, limited education, incarceration, and health illiteracy, as well as race, ethnicity, and language fluency, upon the ongoing disparity in HIV infection among racial and ethnic minorities across the life course.
- Increase emphasis on research to examine the influence of race, ethnicity, and gender, independently and in combination, upon social norms and cultural contexts that affect HIV acquisition, transmission, and risk.
- Design and conduct studies that determine the factors that promote or impede early access to HIV prevention, care, and treatment.
- Recruit and retain racial and ethnic minorities in sufficient numbers to have the statistical power to detect racial, ethnic, and gender differences in NIH-sponsored studies.
- Examine the influence of stigma, racism, homophobia, and racial and cultural stereotyping within these communities, as well as among health care providers and health care systems, upon racial and ethnic minority HIV testing and counseling behaviors.
- Develop effective prevention efforts for high-risk negatives within health care systems for non-HIV-related conditions.
- Identify venues for more acceptable and accessible HIV testing for racial and ethnic minorities. Identify behavioral and structural factors that affect HIV testing frequency.
- Develop and test effective models for increasing awareness of the need for routine and regular HIV testing in racial and ethnic minority communities.
- Evaluate models for HIV prevention with positives utilizing comprehensive, holistic, and culturally and contextually appropriate interventions that include care, support, and treatment.

OBJECTIVE–C

Conduct HIV prevention research that includes racial and ethnic minorities in numbers that reflect the current incidence rates, as well as their trajectory in the domestic AIDS epidemic.

STRATEGIES

- Promote public-private-academic partnerships to study and promote HIV prevention in those communities most heavily affected by HIV infection.
- Translate effective HIV prevention interventions into communities and clinics for the provision of evidence-based services.
- Study the biologic and physiologic factors that affect HIV acquisition, transmission, and resistance to infection in racial and ethnic minorities.
- Support community-initiated HIV prevention research and evaluation studies.
- Explore the impact of social and physical stress upon immune function in HIV-infected and uninfected high-risk individuals in those communities most affected by HIV infection.
- Advance awareness and understanding of the ethics of prevention research, as well as the protections required for research participants in racial and ethnic minority communities, through existing mechanisms of information dissemination.
- Incorporate community-based participatory research ethics into all community-based projects to ensure the bidirectional benefit and investment of the community and the research team, including entering and exiting a community.
- Develop models to better engage communities heavily affected by HIV infection for community-based participatory research.

OBJECTIVE–D

Fund 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

- Examine aspects of HIV risk unique to adolescents and to adolescent behavior, to determine how this affects them, their social peer networks, and HIV acquisition.
- Develop, pilot, and test models of HIV prevention that identify those factors that increase HIV risk among the transgendered, as well as interventions to modify that risk.
- Explore the hormonal, behavioral, social, and cultural factors that affect HIV risk in older women, especially women of color.
- Examine the impact of domestic seasonal migration on HIV risk behavior and comorbid sexually transmitted infections.
- Explore the interface between countries, their borders, and the impact of these borders on HIV risk behavior across borders, as well as access to HIV counseling, testing, and treatment services.
- Develop, pilot, and test HIV prevention interventions for documented and undocumented immigrants for efficient and rapid translation into the field.
- Identify effective and efficient HIV prevention interventions that can be successfully implemented in rural communities.
- Explore social marketing and health communication strategies used by the private sector to develop new interventions for effective HIV prevention in racial and ethnic minority communities.
- Explore the components of effective outreach, and develop models of successful outreach and quantification of that success.
- Examine prevention interventions to define the components of sustainable interventions for heavily affected communities.

Research in International Settings

AREA OF EMPHASIS

Research in International Settings

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A

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, when necessary, 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;
- enhancing mechanisms for information exchange among investigators, including enhanced electronic communication;
- conducting research on how to 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 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 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 for AIDS, Tuberculosis, and Malaria (GFATM), nongovernmental organizations (NGOs), private industry, foundations, and alliances (e.g., Global HIV/AIDS 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 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.

- 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, and governments 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.

- Implement the UNAIDS Guidance Document (specifically, Guidance Point 16) on addressing the provision of antiretroviral treatment for participants following their completion of NIH-funded HIV antiretroviral treatment trials in developing countries (UNAIDS. *Ethical Considerations in HIV Preventive Vaccine Research*. UNAIDS Guidance Document: 2000).
- 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.

OBJECTIVE–B

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 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 policy-level 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.

- Provide sustainable career development opportunities for 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 training, both in-country and in the United States, of clinicians (physicians and nonphysician professionals, e.g., nurses, midwives, etc.), public health professionals, 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 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 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

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, and evaluate the effectiveness of rights-based interventions to improve AIDS outcomes.
- Ensure that all research is conducted in culturally appropriate content, form, and format.
- 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.
- Evaluate the effectiveness of expanded access to male circumcision programs and the policy-level changes necessary to implement such expanded interventions.

OBJECTIVE–D

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

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

STRATEGIES

- Conduct research on sex and gender differences in access and use of prevention and care services.
- 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 gender-specific conditions, such as human papillomavirus (HPV) infection and cervical cancer.
- 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.

OBJECTIVE–E

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.
- 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 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.
- 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

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.

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.
- 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 individ-

uals; 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 Barriers

- Discover and develop candidate microbicides to prevent sexual transmission.
- Conduct Phase I, Phase II, and Phase III clinical trials for safety and efficacy, with appropriate surrogate markers and measures of correlates of protection with suitable candidate microbicides in domestic and international settings.
- Determine the efficacy and use of prevention interventions, including microbicides and other physical/chemical barrier methods, and determine the factors affecting their use.
- 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 and cervical cancer.
- 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 drug users and out-of-treatment drug users.

MTCT: Considerations for the Mother, Child, and Family

- Develop safe, effective, feasible, and conveniently administered strategies to interrupt MTCT, using interventions that are affordable and can be implemented in resource-constrained countries, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactation period.
- Conduct research to identify the obstacles and facilitators for scaling up successful interventions.
- Develop and evaluate strategies for reducing the risk of MTCT, providing safe ART to pregnant women, and assessing the effects of variable-length combination ART to HIV-infected women on both MTCT and the women's own health, including the impact on subsequent pregnancies.
- Study the effects of antiretroviral (ARV) regimens used for maternal health indications on the risk of MTCT (including postnatal transmission through breast milk) and other outcomes, including pregnancy outcomes.
- Investigate the mechanisms and timing of MTCT (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Further identify cost-effective, nondrug regimens for preventing MTCT, such as research on infant feeding, including:
  - acceptability of safe breastfeeding alternatives;
  - impact of the use of breast milk alternatives on morbidity and mortality of both the mother and infant; and
  - role of exclusive breastfeeding.
- Conduct studies to evaluate and reduce short- and long-term toxicities of ARVs in women during pregnancy and in their offspring who were perinatally exposed.
- Investigate the unique immune status of pregnant women and their infants and develop immune interventions to interrupt HIV transmission.

- Examine the role of maternal and infant nutrition during the peripartum and postpartum periods in reducing morbidity and mortality in HIV-infected mothers and their infants and in reducing MTCT.
- Study the impact of the health status of HIV-infected mothers on the survivability of both HIV-infected and HIV-uninfected children.
- Investigate methods to improve reproductive health in serodiscordant couples, including HIV risk reduction in *in vitro* fertilization.
- Study the impact of breastfeeding on the health status of HIV-infected mothers.
- Investigate the risk of MTCT when maternal HIV infection is acquired during pregnancy, including:
  - impact of maternal acute infection on *in utero* risk of MTCT;
  - impact of maternal acute infection on established interventions for preventing MTCT; and
  - development of public health approaches for detecting or reducing maternal incident infection during pregnancy.

OBJECTIVE–G

Develop and evaluate the most effective, setting-specific strategies for care and treatment of HIV-related conditions and their sequelae among HIV-infected and -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, and toxicity of ARVs and prophylaxis medications against major coinfections in adult, adolescent, and pediatric 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., adults, children, and adolescents) 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 models of care, and enhance interdependent programs that integrate AIDS care and existing services, such as tuberculosis

(TB) control programs, alcohol and other substance abuse/dependence treatment programs, maternal and child health services, and support services for the elderly, to avoid duplication of efforts.

- 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 to support adherence in adults, 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 countries and determine the minimal level of ARV resistance monitoring necessary and the methods to be used for such monitoring.

OBJECTIVE–H

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 and neurological conditions) in adult, adolescent, and pediatric populations specific to individual regions in diverse geographic settings.
- Determine optimal ways of integrating treatment for HIV 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 deploy new rapid diagnostic and drug susceptibility tests for TB and new agents and therapeutic strategies to treat drug-sensitive and drug-resistant TB (including MDR-TB and 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.
- 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 coinfected individuals.

OBJECTIVE–I

Evaluate the impact of prevention and treatment programs on the HIV epidemic, taking advantage of comprehensive health service delivery programs related to HIV and AIDS.

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

STRATEGIES

- Assess the impact of ART on risk behaviors, HIV transmission, and prevalence, including associated behavior change, in various communities.
- Determine the social, psychological, societal, and economic impact of ART on individuals (including children), families, and communities, including the impact on personal risk behaviors.
- 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, noninfected 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-discordant 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.
  - 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.
  - 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.