

CHAPTER 5

Research Related to Specific Populations

Women and Girls

Racial and Ethnic Minorities

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 and acquisition among women and girls across the life cycle.

STRATEGIES

- Evaluate HIV transmission and acquisition in relation to viral factors, such as genotype, phenotype (inclusive of drug resistance), clade, viral load, replicative forms, viral fitness, and heterogeneity.
- Identify and characterize cells responsible for viral acquisition and propagation at mucosal surfaces in the oral cavity and the entire reproductive tract (fallopian tubes, uterus, cervix, vagina, vulva) and anal canal.
- Evaluate HIV transmission and acquisition in relation to viral shedding in different mucosal compartments (including semen, cervicovaginal secretions, and saliva).
- Evaluate HIV transmission and acquisition in relation to age, timing, and occurrence of endocrine status changes (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 HIV.
- Evaluate HIV transmission and acquisition in relation to other host factors, such as nutrition, nonhormonal contraception use, anatomic/physiologic changes (female circumcision, cervical ectopy, postdysplasia treatment), and localized inflammation secondary to 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 and transmission.
- 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 and acquisition.

OBJECTIVE–B

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.

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 across the life cycle.
 - ▶ Investigate the role of potential cofactors and mediators of disease progression in both early- and late-stage disease, including hormonal endogenous factors (inclusive of hormonal changes across the life cycle and throughout the menstrual cycle) and exogenous factors (inclusive of 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 sexually transmitted infections (STIs); use and abuse of alcohol and other substances; reexposure to different strains of HIV including drug-resistant strains; age; intermittent therapy and mono-therapy 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 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 gynecologic manifestations and identification and treatment of gynecologic disease 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.
- ▶ Investigate the impact of comorbid conditions on HIV-related manifestations in women and girls, including HCV coinfection and autoimmune disease.
- ▶ Elucidate characteristics of neurologic and neuropsychologic manifestations (dementia, 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, 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, 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–C

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

STRATEGIES

- Evaluate innovative and rapid testing strategies in a range of settings to identify HIV infection in women and girls.
- Study the psychosocial consequences of receiving HIV-positive results on women across the lifespan, including during adolescence, during the reproductive years, and during menopausal and post-menopausal stages of life, and the impact on treatment and care decisionmaking.
- Evaluate the impact of antepartum 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 specifi-

cally, 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 use in treatment and ART pharmacology studies.

OBJECTIVE–D

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

STRATEGIES

- Examine the impact of population-level interventions on HIV acquisition among women and girls, such as social normative behavior changes, programs to increase educational opportunities and economic independence, mass or syndromic approaches to STI control, early diagnosis and treatment of HIV infection and other STIs, use of family planning programs to diagnose and treat STIs, and availability 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 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, 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, war) on HIV risk for women and girls.
- 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–E

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 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, 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, hormonal changes during pregnancy, use of contraceptives or hormonal replacement therapy, and presence of selected STIs.
- Study potential effects of candidate vaccine or microbicidal products on the genital tract immune system and their ability to induce inflammatory activity that might compromise the integrity of the mucosal surface of the genital tract and decrease or enhance the inductive ability of vaccines.

- Study the impact 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.).
- 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–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 decisionmaking.
- Support research to improve understanding of fertility 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 fertility goals without 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; 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, 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 Minorities

AREA OF EMPHASIS

Racial and Ethnic Minorities

SCIENTIFIC OBJECTIVES AND STRATEGIES**OBJECTIVE–A**

Examine sociocultural and structural determinants, social structures, and health systems that enhance, sustain, and/or perpetuate health disparities.

STRATEGIES

- Emphasize basic research and its clinical application to determine the impact of culture, race, and gender upon the response to HIV infection and treatment.
- Explore the effect of poverty, limited education, and health illiteracy, as well as acculturation, language fluency, and access to services, upon the ongoing disparity in HIV infection among immigrants.
- Examine the influence of race/ethnicity and gender, independently and in combination, upon social norms and cultural contexts that affect HIV transmission risk behaviors, as well as HIV disease progression.
- Design and conduct studies that determine the factors that promote and/or impede early access to care and treatment, with attention to individual and health care system factors.
- Develop and enforce mechanisms that share information gathered from trial data with the communities that participated in NIH-funded programs, allowing the collection of such data.
- Encourage, through specific funding initiatives, studies to examine the impact of traumatic stressors upon indigenous domestic populations, including Native Americans and Alaska Natives, such as acculturative stress and intergenerational trauma, upon HIV risk behaviors and HIV health-care-seeking behavior.
- Examine the influence of stigma, racism, homophobia, and racial and cultural stereotypes among health care providers and health care systems (including infrastructure) upon racial and ethnic minority community HIV care access, as well as provision of HIV treatment.

OBJECTIVE–B

Identify and examine the health care, social systems, and structural barriers that promote and sustain the health disparity in HIV infection among racial and ethnic minorities.

STRATEGIES

- Promote and sustain interagency research to:
 - ▶ Determine the impact of the criminal justice system in increasing the risk of HIV transmission among racial and ethnic minorities;
 - ▶ Determine the disease burden accruing within the criminal justice system and the effect of this disease burden upon the health care systems and infrastructure within racial and ethnic minority communities; and
 - ▶ Determine the impact of reentry of HIV-infected individuals from prison to the community upon HIV care provision, as well as antiretroviral drug resistance.
- Determine the impact of combined economic and educational disparities upon the health outcomes of racial and ethnic minorities with HIV infection.
- Examine and evaluate the role of health care disparities and public policy factors in sustaining the disparities in the health outcomes of racial and ethnic minorities with HIV infection.
- Determine the impact of structural factors within health-related organizations, such as insurance status and institutional racism, upon when racial and ethnic minorities present for HIV-related care and its impact upon disease progression.
- Encourage, through targeted funding, interdisciplinary research that develops and tests interventions designed to reduce/eliminate structural factors that impede access to HIV-related care.
- Support studies that examine and quantify the potential impact of incorporating HIV-related services into existing services for reproductive health, family planning, and sexually transmitted infection already placed within racial and ethnic minority communities. This would include the impact upon not only HIV prevention and infections averted, but also HIV detection, care, and community awareness.

OBJECTIVE—C

Enhance and expand the capacity for NIH-funded HIV research by underrepresented minority investigators, institutions, and communities, especially Native American and Alaska Native. Minority is defined as any racial or ethnic group other than Caucasian in the United States.

STRATEGIES**For the investigator:**

- Promote and expand predoctoral opportunities for the development of minority investigators.
- Establish a national mentoring network for the development and retention of racial and ethnic minority investigators in HIV/AIDS research.
- Conduct a review through the Office of Extramural Research, in response to the National Research Council report, to determine the number of minority scientists produced as a result of existing NIH programs (such as the K award, minority biomedical research supplements) to support the transition from trainee to independent investigator, with the goal of enhancing and expanding successful programs.
- Through existing funding mechanisms, provide incentives and support for senior investigators to identify, develop, and mentor racial and ethnic minority investigators in culturally and contextually appropriate HIV/AIDS research domestically and internationally.
- Through existing funding mechanisms, provide incentives for the development, recruitment, and retention of intramural and extramural racial and ethnic minority investigators, including the provision of scholarship support to attend scientific meetings.
- Review existing programs designed to increase the awareness of underrepresented racial and ethnic minority investigators of NIH funding mechanisms for HIV/AIDS research, enhancing those programs that are successful and eliminating those that are not.
- Recreate scientific review panels at the Center for Scientific Review and the Institutes, as current panels reflect neither the demographics of the epidemic nor the populations affected. Annual reporting of the increases in racial and ethnic minority participation on review panels, including ad hoc panels, should be made to the Director of the Office of AIDS Research.

For the institution:

- Increase the number of minority and majority institutional partnerships with shared research interests for research program and infrastructure development, building upon successful existing models such as the National Center for Research Resources.

- Utilize existing funding support to minority-serving and minority-predominant institutions for the development of an HIV/AIDS research agenda, including an assessment of needs.
- Utilize existing funding mechanisms targeted to minority institutions to ensure training and development of sufficient personnel for the successful conduct of HIV/AIDS research.
- Enhance community-academic partnerships by requesting a plan for research development as part of the peer-reviewed application, documenting bidirectional collaboration.
- Foster coalitions and partnership-building with other institutions, across Department of Health and Human Services (DHHS) agencies and stakeholders, to strengthen strategic collaborative efforts to address HIV/AIDS research issues in racial and ethnic minority communities.
- Improve basic science capacity at minority-predominant and minority-serving institutions (including tribal entities) through mentored training awards, infrastructure development, and majority-minority institutional partnerships and collaborations.

For the community:

- Increase minority participation on community advisory boards for HIV research to reflect their current incidence and trends in the epidemic.
- Include community consultations in NIH-funded extramural research from study development to the dissemination of study results.
- Share study results with participants promptly through existing information dissemination mechanisms as well as through community organizations/research partners.
- Fund community-based and community-driven participatory research to facilitate bidirectional transfer of knowledge and observations of interest to both the community and the investigator(s).

OBJECTIVE–D

Conduct HIV research that includes numbers of racial and ethnic minorities that reflect not only the current domestic HIV/AIDS prevalence, but also emerging incidence trajectories in minority subgroups.

STRATEGIES

- Require that clinical trials be appropriately powered to conduct subgroup analyses exploring the potential for differential responses to treatment, metabolic toxicities, drug adverse events, and immune responses in racial and ethnic minorities.
- Facilitate through funding incentives at both the investigator and the research institution levels, academic-community partnerships to enhance clinical trial recruitment and retention of racial and ethnic minorities.
- Advance the awareness and understanding of the ethics of clinical research, as well as the protections required for research participants, in racial and ethnic minority communities through innovative approaches in partnership with the community-based organizations that serve these communities and neighborhood key opinion leaders.
- Examine the impact of exclusion criteria, to determine if any particular population or populations are more frequently eliminated. Propose strategies to protect such populations in order to facilitate their participation in clinical research.
- Evaluate the effects of HIV infection by age and gender upon the physiologic, immunologic, hormonal, and neuropsychological development of racial and ethnic minority adolescents for potential therapeutic interventions.
- Develop, test, and support creative clinical research methodologies that examine prospectively racial/ethnic/gender/sexual orientation differences in transmission, pathophysiology, and treatment outcomes.
- Determine the impact of race-related factors in understudied indigenous populations, including Native Americans, Alaska Natives, Pacific Islanders, and Native Hawaiians.
- Identify the factors that influence HIV transmission among racial and ethnic minorities.
- Examine the impact of alcohol, drug use, and chronic medical and neuropsychiatric comorbidities on the success or failure of HIV clinical interventions and HIV disease progression in racial and ethnic minorities.
- Continue exploration of proteomics and genomics to determine the individual and combined effects of race, gender, and age upon immune response and response to treatment.

- Advance the study of the biology of HIV infection among racial and ethnic minorities by:
 - ▶ Evaluating the effect, if any, of race/ethnicity and gender upon immune dysfunction and the development of opportunistic infection;
 - ▶ Determining the effect of race/ethnicity and gender upon p-glycoproteins and their role in the individual response to HIV therapy and the development of HIV drug resistance; and
 - ▶ Exploring the role of preexisting health conditions disproportionately found in racial and ethnic minorities, such as cardiovascular disease, diabetes, and hepatitis, upon HIV disease course and progression.
- Develop, test, and promote successful strategies for linking community organizations with NIH research performance sites through the use of Internet resources, such as AIDSinfo.nih.gov.

OBJECTIVE—E

Explore the effect of HIV infection as a chronic disease with long-term consequences upon racial and ethnic minority individuals, as well as their communities.

STRATEGIES

- Determine the impact of preexisting and coexisting disorders such as alcohol use and abuse, substance abuse, hepatic infections, sexually transmitted infections, and mental health disorders upon HIV infection and progression, to develop and implement successful intervention strategies.
- Fund research that explores factors that prevent chronic HIV disease, including:
 - ▶ The role of extended and nuclear family and caregivers;
 - ▶ The role of traditional and nontraditional organizations upon social structure and norms;
 - ▶ The role of peer and social networks; and
 - ▶ Individual, as well as community, interface with health care delivery systems.
- Study the impact of alcohol, substance abuse, and mental health treatment as an approach to HIV prevention.
- Expand research to identify specific points for intervention in racial and ethnic minority communities to prevent the long-term sequelae of sexually transmitted and HIV infections by:
 - ▶ Identifying the barriers to participation in microbicide and vaccine trials among racial and ethnic minorities, and testing interventions to overcome these barriers;
 - ▶ Enhancing research on the potential impact of vaccines and microbicides upon HIV transmission among racial and ethnic minorities; and
 - ▶ Promoting research to identify successful interventions to promote access to, as well as retention in, HIV treatment.
- Promote research on HIV infection among older racial and ethnic minority individuals with and without preexisting chronic conditions, and the impact of overall general health status upon HIV transmission in these individuals.
- Determine the impact of HIV infection upon functional expression, including quality of life, function, functional status, and the aging process.

OBJECTIVE—F

Develop and test innovative research, models, methods, and measures to accurately assess risk behavior.

STRATEGIES

- Develop, pilot, test, and evaluate new measures of HIV risk behavior that investigate the influences of culture and context on the behaviors of 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.
- Develop new models of HIV behavioral interventions that take into account the interrelated risks associated with substance abuse, socioeconomic status, trauma, and cultural and gender identity.
- Develop novel sampling methods to enhance the representation of racial and ethnic minorities in clinical research, with attention to sampling adequately from indigenous populations.
- Fund through specific announcements the development and testing of new sampling methodologies in racial and ethnic minority communities.
- Identify resiliency and protective factors found in racial and ethnic minority communities, and test them for their impact upon decreasing HIV transmission.
- Validate existing measures for language translation accuracy and for cultural and linguistic equivalents for each of the racial and ethnic minority communities in which they are to be used.
- Identify sampling methods and intervention models that measure racial and ethnic minority subpopulation differences in behavioral risks and outcomes.
- Fund the development and standardization of assessment tools that are designed for the racial and ethnic minority community in which they are to be used.
- Study HIV risk behaviors of underrepresented racial and ethnic minorities, such as Native Americans, Alaska Natives, and Asian Pacific Islanders, including the role of intergenerational trauma and acculturative stress.

OBJECTIVE–G

Identify factors that contribute to delay in the diagnosis of HIV/AIDS in racial and ethnic minority communities and hence contribute to delays in treatment. Investigate public health, community, and individual approaches that will facilitate earlier identification of HIV infection, as well as prompt access to treatment and care.

STRATEGIES

- Determine the effect of stigma (expressed and perceived), race, ethnicity, gender, and sexual orientation upon delayed testing for HIV infection, delayed treatment, and adherence to treatment.
- Identify factors at the individual, societal, and community level that promote HIV testing, treatment, and adherence; develop interventions to determine their effectiveness in racial and ethnic minority communities.
- Study the impact of provider decisionmaking, as well as provider-patient interactions, that negatively and positively affect the decision to consent to HIV testing and treatment in racial and ethnic minorities.
- Define the role and impact of health beliefs and prior experiences with the health care system upon HIV testing, treatment acceptance, and treatment adherence in racial and ethnic minorities.
- Explore the use of complementary and alternative therapies in racial and ethnic minority communities as an alternative to seeking care in conventional health settings due to stigma, fear, or mistrust.
- Maintain research upon the impact of complementary and alternative therapies upon treatment adherence for HIV infection, symptom relief, and the complications of HIV infection.
- Fund studies of community-based multilevel interventions to promote HIV testing, care seeking, and treatment.

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 both Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) requirements for large-scale clinical trials, through:
 - ▶ strengthening laboratory capacity 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 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 Health Resources and Services Administration (HRSA), and the State Department.
- Work with foreign governments, international organizations (e.g., the World Health Organization [WHO], with particular emphasis on coordinating research and research infrastructure development with WHO's 3x5 Program), 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 HIV/AIDS care and prevention; to facilitate their involvement as partners and indigenous health professionals in global HIV/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 *Guidance for Addressing the Provision of Antiretroviral Treatment for Trial Participants Following their Completion of NIH-Funded HIV Antiretroviral Treatment Trials in Developing Countries*.
- 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.
- 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 and malignancies, including research training related to (1) treatment and care, (2) clinical trials of therapeutic strategies for HIV and endemic coinfections, (3) development and testing of vaccine candidates, (4) impact of alcohol and other substance abuse/dependence on HIV transmission, (5) reproductive health, including microbicides, (6) disease progression, (7) prevention of mother-to-child transmission (MTCT), and (8) other biomedical, social, and behavioral prevention research.
- 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, 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 HIV/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 better 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; 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.
- Ensure that all research is conducted in culturally appropriate content, form, and format.
- Evaluate the effectiveness of expanded access to needle and syringe exchange programs and the policy-level changes necessary to implement such expanded interventions.

OBJECTIVE–D

Support HIV/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.
- Study gender-related biological factors affecting susceptibility to HIV infection, including the use of hormonal contraceptives 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 (i.e., 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) regimens.

OBJECTIVE—E

Study the significance of interactions among individuals in various risk groups, 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 (individual, couple, group, 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 the social networks of injection and noninjection drug users and heavy drinkers 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.

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, 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 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 Barriers

- Discover and develop candidate microbicides to prevent sexual transmission.
- 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

- 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 approaches for drug and alcohol abuse programs among HIV- and HCV-coinfected patients to improve adherence with drug/alcohol treatment strategies.
- Develop innovative strategies for identifying “hidden populations” of young drug users and out-of-treatment drug users.

MTCT: Considerations for the Mother, Infant, and Child

- 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.
- 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.
- 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.

(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 opportunistic infections (OIs) prophylaxis medications 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.
- 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 care models, such as family models of care, and enhance interdependent care services that integrate AIDS care into existing programs, such as tuberculosis (TB) control programs, alcohol and other substance abuse/dependence treatment programs, and maternal and child health services, 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 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.
- Develop and evaluate suitable, sustainable approaches for diagnosis of HIV infection, monitoring treatment safety and efficacy, side effects, and toxicities, with particular emphasis on finding affordable technologies to measure CD4+ cell counts and HIV load, as well as suitable 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 and endemic diseases, and develop strategies to optimize diagnosis, treatment, and care.

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

STRATEGIES

- Examine the role of coinfection with other endemic diseases and their treatment in modulating HIV infection or disease, including risk of acquiring and/or transmitting HIV infection and disease progression.
- Investigate the impact of coinfections with other endemic diseases and their treatment on 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.
- 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, 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 and coinfections, especially TB, including clinical research to assess clinical outcome and operational research to determine cost-effectiveness.
- Investigate sustainable strategies for preventing, treating, and monitoring response to treatment of endemic coinfections in HIV-infected adults, adolescents, children, and infants in resource-constrained 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, and malaria) in the adult, pediatric, and adolescent populations infected with HIV.

- 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/prophylaxis for endemic coinfections in HIV-infected individuals.
- 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 coinfections and opportunistic infections.
- Assess the burden of TB and the relative importance of reactivation versus *de novo* infection in HIV-coinfected individuals in various settings.
- Identify affordable strategies to target high-risk patients for initiation of prophylaxis for HIV-related coinfections and OIs.
- Conduct studies to better understand the role and mechanism of reinfection and/or superinfection with HCV in coinfecting 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/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 scaleup 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.