

PRIORITY:

Reducing HIV-Related Disparities

Special Populations:

Racial and Ethnic Populations

Women and Girls

Research in International Settings

Training, Infrastructure, and Capacity Building

AREA OF EMPHASIS

Racial and Ethnic Populations

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE—A: System Determinants of Health

Support research that examines the impact of policies, organizations, financing, and delivery of HIV/AIDS-related prevention, care, treatment, and support services in disproportionately affected racial and ethnic populations, including those demonstrably at highest risk for HIV infection.

STRATEGIES

- Identify and modify system-level factors that mitigate or create barriers to HIV prevention, care, and treatment for incarcerated racial and ethnic minorities when they return to their communities.
- Explore the systems of care available to seasonal workers and what factors facilitate and prevent engagement in HIV testing, care, and treatment.
- Identify and modify system-level factors that mitigate or create barriers to HIV testing, care, and treatment for aboriginal individuals, including the role of traditional and/or indigenous medicine.
- Utilize implementation science to identify the essential components of HIV prevention interventions and mechanisms for efficient and rapid translation among racial and ethnic minority populations.
- Develop, pilot, and test synergistic prevention interventions for high-risk HIV-uninfected individuals within health care systems.
- Examine the influence of stigma, racism, prejudice, and homophobia within health care systems, and the impact of these biases upon HIV prevention behaviors (including HIV testing) among racial and ethnic populations.
- Identify venues that can effectively deliver acceptable, efficient, and dependable HIV testing for racial and ethnic populations.

OBJECTIVE–B: Environmental and Social Determinants of Health

Encourage research that identifies specific environmental and societal factors, including economic disadvantage, racism, sexism, and homophobia, that drive: (1) HIV-risk behavior; (2) HIV acquisition, transmission, and disease progression (including the development of viral resistance); and (3) adoption and incorporation of effective prevention and therapeutic interventions for those at highest risk for HIV infection.

STRATEGIES

- Explore the intersections of the social determinants of health (such as poverty, residential segregation, and incarceration), and their effects upon HIV transmission across the lifespan.
- Identify synergistic effects of the provision of stable housing, treatment, and prevention interventions upon HIV-risk behavior, disease outcome, and treatment.
- Examine the influence of race, ethnicity, language fluency, and gender, independently and collectively, upon the social and cultural contexts of HIV acquisition, transmission, and risk.
- Examine the impact of the intersections of poverty, racism, substance abuse, and historical displacement upon HIV-risk behavior and HIV resiliency in indigenous populations,
- Study the impact of social, sexual, alcohol, and drug networks upon the HIV risk among racial and ethnic youth.
- Develop culturally and racially appropriate HIV testing and prevention interventions targeting adolescents and youth for dissemination in their social and sexual networks.
- Explore the impact of immigration status, including seasonal population migrations (e.g., migrant workers), upon HIV-risk behavior and comorbid sexually transmitted infections (STIs).
- Identify HIV prevention interventions for rural undocumented immigrant communities.
- Examine the impact of prejudice, racism, stigma, and racial stereotyping by health care providers on access to HIV prevention, care, and treatment.

OBJECTIVE—C: Family and Community-Level Determinants of Health

Expand research that focuses on HIV-related community capacity, preparedness, and/or response readiness (e.g., readiness to adopt specific prevention intervention measures). This includes the familial, cultural (traditional and indigenous), and community-level factors associated with HIV infection, risk of infection, and related health outcomes in racial and ethnic populations.

STRATEGIES

- Identify practical, cost-effective, sustainable, and scalable community-level HIV prevention interventions for racial and ethnic communities, including sexual minorities.
- Develop, test, and pilot multidisciplinary HIV prevention and treatment interventions that target intersecting antecedents of HIV transmission (e.g., incarceration and drug use, poverty, and homelessness).
- Develop measures of community engagement (e.g., with leaders and organizations) that predict readiness for, and acceptance of, evidence-based prevention interventions.
- Identify the factors that consistently predict the level of community readiness to engage with HIV prevention research.
- Study the intersection between community and health organizations required for effective prevention message delivery, including the role of key informants, key community organizations, and the linkages necessary for community acceptance.
- Develop models to incorporate community-initiated HIV prevention interventions and evaluation into community-based participatory research, especially in communities disproportionately affected by HIV.
- Incorporate implementation science in the development of HIV prevention interventions to facilitate prompt translation, scale-up, and delivery of effective interventions.
- Examine the impact of existing and evolving social and sexual norms and community-derived responses to the HIV epidemic on changing patterns of sexual risk behavior.

OBJECTIVE–D: Individual-Level Determinants of Health

Develop and conduct research that focuses on individual-level determinants of HIV risk, including biologic factors, resiliency, and cultural and social norms, in disproportionately affected populations.

STRATEGIES

- Develop, pilot, and test synergistic prevention interventions for high-risk HIV-uninfected individuals within health care systems.
- Identify factors (e.g., health literacy and HIV awareness) that increase HIV risk among disproportionately affected populations, and examine the impact of HIV preventions that reduce or eliminate those factors.
- Identify the behavioral, biological, cultural, and social factors that affect older women and affect their risk of HIV acquisition and transmission.
- Conduct basic research on and develop interventions that address the social and ecological determinants of sexual health and HIV risk in disproportionately affected populations and their social networks.
- Determine the impact of personal trauma (e.g., gender-based violence and childhood abuse) upon the adoption and maintenance of HIV prevention strategies in racial and ethnic populations, with particular attention to adolescents and sexual minorities.
- Study the biological (including genetic), physiological, and environmental factors that affect HIV acquisition, transmission, and disease progression among racial and ethnic minority individuals.

OBJECTIVE–E: Expanding Research Methods and Measures

Develop and test innovative methods and measures to accurately assess the system, social, community, and individual determinants of HIV risk in racial and ethnic populations, with special emphasis on those underrepresented in current clinical studies.

STRATEGIES

- Recruit and retain racial and ethnic minorities, using existing and novel sampling methods to ensure numbers sufficient to provide adequate statistical power to detect racial and gender differences in NIH-sponsored studies, especially Phase III clinical trials.
- Fund initiatives to develop novel sampling methods to enhance the proportion of underrepresented populations that are disproportionately affected by HIV infection in clinical and prevention research.
- Develop and standardize assessment tools for rural populations, populations with foreign-born individuals, and racial and ethnic populations at risk for HIV acquisition.
- Develop, pilot, test, and evaluate new measures of HIV-risk behavior that are culturally and contextually appropriate for racial, ethnic, and sexual minority populations.
- Develop novel methods of delivering HIV care and treatment interventions in nontraditional venues for racial and ethnic populations, including those that utilize social networks and technology to enhance community penetration and effectiveness.
- Develop measures to assess the impact of evidence-based quality-of-care and best practices upon HIV disease outcome in racial and ethnic minority individuals.
- Develop novel clinical research methodologies for prospective studies of the effect of racial, ethnic, gender, and sexual orientation differences on HIV transmission, disease pathophysiology, and treatment outcomes.
- Utilize implementation science to identify what determines which HIV prevention interventions are ready or necessary for efficient and rapid translation into the field.
- Develop, pilot, and test models of HIV behavioral interventions that incorporate common resiliency factors for racial and ethnic populations, such as cultural identity, spirituality, family ties, and collectivism.

OBJECTIVE–F: Treatment and Treatment Access

Support behavioral, intervention, and implementation research that: (1) creates and tests interventions to modify the factors that prevent access to care, treatment adherence, and care maintenance; (2) examines biological and individual factors that affect response to HIV treatment and its associated complications and comorbidities; and (3) determines critical junctures where effective interventions will result in improved treatment outcomes in disproportionately affected racial and ethnic populations.

STRATEGIES

- Advance the study of the biology of HIV infection among racial and ethnic populations:
 - ▶ Evaluate the effect of race, ethnicity, and gender upon immune response to combination antiretroviral therapy.
 - ▶ Determine the effect of race, ethnicity, and gender upon immune dysregulation and the development of opportunistic infection and malignancies.
- Determine the impact of race and ethnicity on risk of HIV acquisition, rate of HIV disease progression, and HIV disease manifestations in understudied indigenous populations, including Native Americans, Alaska Natives, Pacific Islanders, and Native Hawaiians.
- Create and test effective interventions designed to increase the uptake of HIV care and enhance the quality of HIV care among racial and ethnic populations.
- Examine the effect of perceived and enacted HIV stigma, as well as homophobia and institutionalized racism, upon access to care, HIV care seeking, care retention and maintenance, and treatment adherence.
- Develop and evaluate therapeutic strategies to prevent and treat the most prevalent complications and comorbidities of HIV infection among racial and ethnic populations.
- Create, test, and disseminate effective multidisciplinary interventions that reduce barriers to HIV care and treatment.
- Enhance and expand research collaborations with tribal entities, community-based organizations, and nontraditional community partners to conduct treatment and treatment adherence research in racial and ethnic populations.
- Enhance and expand recruitment and retention efforts to increase the participation and retention of migrant workers in HIV clinical trials, with a specific focus upon HIV prevention, treatment access, treatment adherence, and retention in care.

OBJECTIVE–G: Comorbidities—The Intersection of Multiple Health Disparities

Explore the interrelationship between HIV infection and a broad range of comorbidities in racial and ethnic populations to: (1) determine their impact upon HIV care, treatment adherence, care retention, and disease progression; (2) modify the impact upon adherence to HIV treatment and the comorbid condition(s); (3) reduce their negative impact upon retention in care; and (4) improve health outcomes for this population.

STRATEGIES

- Determine the impact of alcohol, drug use, and chronic medical and neuropsychiatric comorbidities upon HIV health care behavior, including medication adherence and retention.
- Delineate the impact of substance use and chronic mental health comorbidities (including chronic pain states) upon HIV disease progression, morbidity, and mortality.
- Determine the impact of treatment interventions upon progression of HIV disease and HIV-associated coinfections and comorbidities, such as hepatitis B and C infection, tuberculosis (TB), STIs, and malignancies.
- Create, test, and disseminate cost-effective provider- and patient-targeted interventions that facilitate access to HIV care and treatment and retention in care.
- Examine the impact of incarceration upon stage at presentation for care, disease progression, and morbidity and mortality of HIV and other comorbid diseases.
- Evaluate the impact of underlying cardiovascular, endocrine, metabolic, neurologic, psychiatric, and renal disorders upon treatment readiness, acceptance, and effectiveness.
- Determine the impact of combination antiretroviral therapy (ART) in late testers on the progression of comorbid conditions, especially hepatitis B and C infection, TB, and malignancies.
- Examine the response to combination ART by race and gender to determine if differences exist and, if present, the causes of these differences and potential interventions.

OBJECTIVE–H: Enhancing and Expanding Capacity for NIH-Funded HIV Research

Enhance and expand the capacity for NIH-funded HIV research by and for individuals from diverse groups disproportionately affected by HIV infection, *and* underrepresented groups such as tribes and tribal entities.

STRATEGIES

For the investigator:

- Promote and expand predoctoral opportunities for the recruitment, training, and retention of investigators from underrepresented racial and ethnic backgrounds.
- Improve HIV/AIDS research capabilities by establishing a national mentorship network to recruit, train, and retain investigators from groups underrepresented in the biomedical sciences.
- Support senior investigators with robust research infrastructures to mentor prospective researchers from underrepresented groups in the biomedical sciences, in culturally and contextually appropriate HIV/AIDS research.
- Through existing funding mechanisms, provide incentives for the development, recruitment, and retention of intramural and extramural investigators from underrepresented groups in the biomedical sciences.

For the institution:

- Utilize existing HIV/AIDS Centers of Excellence and networks for training and mentorship of postdoctoral fellows, as well as M.D.–Ph.D. fellows from groups underrepresented in biomedical sciences.
- Support collaborative efforts among research-intensive and non-research-intensive institutions to encourage and enhance interest in the conduct of HIV/AIDS research.

- Support activities and programs (e.g., workshops, curriculum improvements, and seed support) in HIV/AIDS to strengthen the representation of disproportionately affected populations in pipeline programs throughout all levels of the institution.
- Support community–academic partnerships and coalitions, as well as partnership-building activities with other agencies across the U.S. Department of Health and Human Services, to strengthen strategic collaborative HIV/AIDS research efforts in disproportionately affected populations.

For the community:

- Develop processes that facilitate the incorporation of new scientific findings into ongoing HIV prevention programs.
- Promote organizational capacity to enhance participation of tribes and tribal entities, and other racial and ethnic community groups, in decision-making to influence programmatic adaptation of new scientific findings.
- ▶ Fund community-based and community-driven participatory research to facilitate: (1) community capacity development, (2) bidirectional transfer of knowledge and observations of interest to both the community and the investigator(s), and (3) culturally and contextually appropriate translation of these findings into community programs.

For systems:

- Determine the impact of system-level factors such as health provider attitudes that prevent HIV-infected individuals from seeking and obtaining needed services.
- Support aspects of the health system composition (e.g., service delivery, convenience of location, hours of operation, and availability of ancillary services) that facilitate accessing health care.
- Identify, implement, and support information-sharing capabilities to promote the development of evidence-based HIV service delivery models for disproportionately affected populations.

AREA OF EMPHASIS

Women and Girls

FY 2013 RESEARCH PRIORITIES

- Design and conduct studies that integrate the biological, behavioral, and social sciences to explain factors that influence HIV risk, pathogenesis, and prevention in women, girls, and infants.
- Define the normal and abnormal biology of the genital and anal/rectal tract across all age groups (including, but not limited to, the changing immunologic and hormonal status), and its relationship to HIV risk, acquisition, and treatment.
- Define the impact of host and viral factors on comorbidities in women and girls.
- Study interactions of HIV and HIV treatment with reproductive health, reproductive technology, and family planning.
- Design and conduct studies that assess the impact of social and behavioral aspects of stigma, discrimination, and disenfranchisement on HIV testing, treatment, and care uptake and delivery across the life cycle.
- Evaluate methods to accurately assess current HIV seroincidence and seroprevalence of women and girls.

OBJECTIVE–A: Determinants of HIV Transmission

Define the mechanisms by which innate and biologic targets for intervention and adaptive viral and host immune factors influence HIV transmission, acquisition, and resistance to infection.

STRATEGIES

- Evaluate the role of viral characteristics and host immune function in HIV transmission, acquisition, and resistance to infection.
- Investigate the relationship of age and endogenous and exogenous hormone status on HIV transmission, acquisition, and resistance to infection.
- Evaluate the role of anal/rectum and genital tract physiology, innate and adaptive immunity, microbiology, and concomitant infections on cellular and other tissue mechanisms on HIV transmission, acquisition, and prevention.
- Study the role of genetic factors in HIV transmission, acquisition, and resistance to infection.
- Study the factors associated with sexual activity on HIV susceptibility, transmission, acquisition, and resistance to infection.
- Study the impact of antiretroviral therapy (ART) on genital tract and anal/rectum viral dynamics and immune function on HIV transmission, acquisition, and resistance to infection.
- Identify and study appropriate animal models to explain female-specific, host-viral-immune interactions and mechanisms of infection in women and girls.
- Develop standardized assays and techniques for sampling upper and lower genital tract, anus/rectum, and oral mucosa to assess host and viral immune factors and physiology that affect HIV transmission, acquisition, and resistance to infection.

OBJECTIVE–B: Integrated Biomedical, Behavioral, and Social Science Prevention Interventions

Conduct and support integrated biomedical, behavioral, and social science interventions research to prevent HIV transmission, acquisition, and resistance to treatment.

STRATEGIES

- Support integrated approaches to combination HIV, sexually transmitted infection (STI), and family planning prevention research that consider the social and cultural context of the population in which the interventions will be applied.
- Support integrated research to understand how health care services, including reproductive health and social services, affect HIV risk, transmission, acquisition, and resistance to infection.
- Analyze the impact of community-level social and behavioral norms on the acceptability and efficacy of and adherence to HIV/STI prevention interventions.
- Analyze the impact of HIV prevention interventions conducted in males on HIV and STI acquisition in females.
- Develop and evaluate methods to recruit and retain women and girls who are demographically representative of the populations at risk for HIV infection into HIV prevention studies.
- Support research to identify effective methods to improve the translation and implementation of female-focused, effective HIV prevention technologies.
- Support research to identify and develop methods to overcome barriers to enrolling girls under the age of 18 and hard-to-reach populations into HIV prevention intervention trials.
- Develop and evaluate interventions that target HIV-serodiscordant couples to prevent HIV and STI transmission and prevent or allow pregnancy.
- Investigate the interaction between HIV-risk perception and sexual behaviors and activity, on the use and effectiveness of HIV prevention methods.
- Conduct and support intervention research to address the couple-specific dynamics that affect HIV risk, acquisition, and transmission.
- Develop, evaluate, and implement culturally focused prevention interventions for populations traditionally perceived to be at low risk for HIV infection.
- Study the impact of macro events and social unrest such as (but not limited to) natural disasters, trauma, war, and refugee status on HIV risk and acquisition for women and girls globally.
- Conduct research on the dynamics of sex- and gender-specific stigma and discrimination, and its impact on HIV risk and prevention.
- Conduct research on the dynamics of sex- and gender-specific violence on HIV/STI risk and prevention.
- Develop, evaluate, and implement HIV/STI prevention interventions that decrease the impact of violence and power discordance on HIV/STI risk.
- Develop and evaluate interventions to reduce or prevent adverse psychological and social consequences for women and girls infected with or affected by HIV/AIDS.

OBJECTIVE–C: Biology of HIV Disease

Study the biology of HIV disease and related coinfections in pregnant and non-pregnant women and girls across the life cycle.

STRATEGIES

- Develop and evaluate innovative and rapid testing strategies in diverse settings to identify acute and chronic HIV infection and HIV-related coinfections in women and girls.
- Identify the mechanisms specific to women and girls that mediate virus/host interactions and affect disease progression, including, but not limited to:
 - ▶ Endogenous and exogenous hormones;
 - ▶ Intermittent ART for the prevention of perinatal transmission; and
 - ▶ Genetic factors.
- Elucidate the sex-specific risks, etiologies, and pathogenesis of HIV disease, disease manifestations, and interactions between HIV and non-HIV-related diseases and conditions.
- Investigate the impact of HIV and HIV-related coinfections and therapy on fetal, infant, and childhood development.
- Evaluate the impact of maternal HIV and ART on breast milk and on breastfed infants.
- Examine the association between sex-specific physical and psychosocial consequences of HIV disease and the initiation and maintenance of HIV-related care.

OBJECTIVE–D: Treatment and Care of HIV Disease

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

STRATEGIES

- Develop and evaluate innovative combination strategies in diverse settings to diagnose, link, and maintain HIV-infected women and girls in HIV care and treatment.
- Study the effect of receiving an HIV-positive test result on HIV-risk behaviors, seeking access to and participating in HIV treatment and care, and in reproductive health.
- Study the pharmacokinetics, pharmacodynamics, toxicity, and success and failure of therapeutics for HIV, opportunistic infections, and other comorbidities in women and girls.
- Evaluate the short- and long-term effects of anti-HIV therapy on health, fertility, morbidity, and mortality in women and girls across the life cycle.
- Study factors that affect adherence to HIV therapeutic regimens and care, and develop and evaluate interventions to improve adherence.
- Evaluate the impact of comorbidities, including substance abuse and mental health disorders, on morbidity, mortality, access to health care, and the enrollment of women and girls in clinical trials.
- Support multidisciplinary research to identify unmet needs and barriers for women and girls to achieving optimal HIV/AIDS care, support, treatment, and prevention services.
- Study the interrelationships between HIV and human papillomavirus (HPV), as well as HIV and HPV vaccination, on HIV risk and pathogenesis.
- Study how treatment interventions in acute and chronic HIV infection, including treatment during pregnancy, affect short- and long-term HIV disease progression.
- Identify appropriate female-specific HIV quality-of-care indicators and study the impact of implementing quality-of-care guidelines on community and country-level health status of women and girls.
- Study the issues relevant to stigma and discrimination and comorbidities that affect women and girls' access and use of health services, including HIV treatment.
- Develop and evaluate accessible assisted reproductive technologies designed to assist in meeting fertility desire without vertical or horizontal HIV transmission.
- Investigate the interaction between HIV, its treatment, and aging and age-related conditions or comorbidities.
- Develop treatment and technological interventions to prevent mother-to-child transmission (MTCT) of HIV through breastfeeding.
- Study the impact of interventions to prevent MTCT and HIV-related comorbidities on the health of women and infants/children, including maternal and infant morbidity and mortality, and on long-term morbidity and mortality.

OBJECTIVE–E: Ethical Issues

Conduct and support research, training, and education on ethical issues that affect the access to and participation of women and girls in HIV/AIDS-related research.

STRATEGIES

- Develop and evaluate strategies to facilitate obtaining fully informed consent from potential clinical trial participants.
- Investigate the unintended consequences of policies and practices for women and girls as a result of their participation in research.
- 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.
- Study the ethical issues related to HIV-specific prevention, diagnostic, and therapeutic strategies implemented during pregnancy and lactation.
- Study the ethical issues related to providing reproductive health services and breastfeeding alternatives in communities where these interventions may not be acceptable.
- Study the ethical issues related to the participation of women and girls in clinical trials.

AREA OF EMPHASIS

Research in International Settings

FY 2013 RESEARCH PRIORITIES

- Continue to develop in-country leadership and support sustainable capacity in HIV/AIDS research in low- and middle-income countries through strengthened research training, building of research infrastructure, and implementation and evaluation of new training methodologies (such as Web-based and distance learning) in cross-disciplinary collaboration with other partners.
- Design and evaluate the integrated application of effective tools and sustainable approaches, in combination and at multiple levels, with a particular emphasis on sociobehavioral and structural interventions targeted to specific settings and/or populations at risk, to prevent HIV infection and transmission.
- Identify more effective care and treatment approaches, integrated with prevention and operational strategies based on implementation science and evaluation research, to ensure epidemic control, reduce HIV-related morbidity and mortality, and maximize cost-effective health outcomes in affected individuals and communities.
- Strengthen in-country laboratory capacity, particularly to refine and validate assays and approaches to identify recent HIV infection and develop accurate incidence density measures across HIV-1 subtypes, host populations, and epidemic stages, and to improve diagnostics for HIV-related coinfections and comorbidities.

OBJECTIVE–A: Capacity Building

Continue to strengthen sustainable and collaborative research environments by building on existing scientific and public health institutions and enhancing in-country leadership and research capacity.

STRATEGIES

Site Development

- Monitor existing international study sites supported by the NIH, and, as needed, further develop sustainable sites, or establish new in-country sites, to address urgent or unmet needs and emerging scientific opportunities, in coordination with ongoing NIH-funded research programs.
- Enhance capacity for the conduct of basic and applied prevention and treatment research through:
 - ▶ strengthening laboratory capacity through the provision of required equipment and human resource development with appropriate quality assurance and training;
 - ▶ maintaining and developing both Good Laboratory Practice and Good Clinical Practice requirements for large-scale clinical trials;
 - ▶ developing diagnostic and clinical capabilities through research training and “hands-on” research experiences;
 - ▶ developing affordable, effective alternatives to viral load, CD4+ cell counts, resistance testing, and other expensive laboratory tests used for monitoring treatment efficacy and toxicity;
 - ▶ developing alternative technologies and assays for the diagnosis and monitoring of HIV-related coinfections (e.g., tuberculosis) and opportunistic infections (OIs) in resource-limited settings, with a goal to be more affordable, simpler (i.e., not requiring electricity, refrigeration, and/or computer), more environmentally durable (i.e., withstanding high ambient temperature, humidity, and dust) than current technologies, and requiring less operator training;
- ▶ enhancing existing pathology practices to permit use of updated disease classification in the diagnosis, ascertainment, and research of HIV-associated comorbidities, particularly in regions such as sub-Saharan Africa;
- ▶ supporting the analysis of scientific and research-based international databases and developing common laboratory information management systems;
- ▶ addressing barriers in establishing, maintaining, optimizing, and ensuring human subject protections related to repositories of biological specimens in resource-constrained countries;
- ▶ developing and testing strategies that support the recruitment and retention of participants in prevention, treatment, and care studies;
- ▶ optimizing epidemiological assessments of targeted at-risk populations, including refining approaches to population-based recruitment of hard-to-reach populations, such as respondent-driven sampling, venue-time sampling, and Internet-based sampling;
- ▶ addressing regulatory issues and oversight mechanisms related to biomedical and behavioral clinical research;
- ▶ conducting research on the feasibility, success, and sustainability of rapid scale-up of pilot projects and/or early Phase I and II trials to large research studies (including Phase III trials) and on how to apply and implement research findings in intended populations;
- ▶ enabling communities to participate appropriately and meaningfully in the development and design of HIV-related research (including clinical trials), as well as in the translation of research results into community-relevant programs, standards of care, and practices;

- ▶ enhancing capabilities in medical records management, data analysis, and biostatistics;
 - ▶ strengthening library services, access to scientific resources, and enhanced information exchange, including electronic communications; and
 - ▶ strengthening capabilities of in-country staff in financial/grants management, administrative practices, and scientific/peer review.
- Continue to strengthen the capacity to conduct implementation science and operational research, including outcome studies, cost-effectiveness analysis, and modeling to rapidly address emerging priorities in prevention, treatment, and care in low- and middle-income countries.
 - Conduct studies on HIV incidence and feasibility, using appropriate incidence measures (e.g., population-specific assays), in order to identify sites suitable for the conduct of efficacy trials of HIV prevention, treatment, and care interventions.
 - Coordinate with other U.S. Government agencies, foreign governments, universities, and international organizations to help identify and support priorities for research infrastructure and capacity building in developing countries.
 - Continue to collaborate with nonphysician health professionals (e.g., nurses, pharmacists, and health aides) and community members (including faith and religious communities, elders, indigenous/traditional healers, student leaders, peer educators, and at-risk populations) to identify practices that may add value in treating and preventing diseases in diverse geographical settings and to facilitate their involvement as partners in AIDS research, prevention, and care, including the optimization of antiretroviral therapy (ART) rollout in settings with limited numbers of physicians and/or resources.
 - Foster regional approaches to research in order to enhance communication, achieve economies of scale, help establish new collaborations, and address common issues and needs (i.e., gap analysis) related to HIV-related research among countries in a given region.

Collaboration and Coordination

- Ensure the leadership role of in-country investigators, academic leadership, community-based and indigenous leaders, and other stakeholders by involving them in all stages of research, including conceptualization of the research question, study design, development of protocols, study implementation, data collection and analysis, publication, and presentation of research results to government and other relevant stakeholders and audiences.
- Encourage the integration and coordination of research projects being conducted by NIH-funded researchers in resource-limited settings with established in-country programs, while collaborating with local investigators, to ensure project relevance and to optimize the research effort.
- Encourage the continued development of research collaborations between U.S. and low- and middle-income institutions and investigators into more equal partnerships, including strategic planning for research.

Ethical Issues

- Ensure that research projects are designed to benefit and engage the communities in which the research is being conducted by addressing locally relevant scientific questions and capacity needs.
- Enhance the capability of institutions in resource-limited settings to conduct independent scientific and ethical reviews, while ensuring timeliness of the review process.
- Strengthen the capacity of institutional review boards (IRBs), including information-sharing between IRBs, updates on recent developments, and monitoring of approved protocols.
- Ensure collaboration between resource-limited countries' ethical review committees and U.S. IRBs, and inform U.S. IRBs about culturally relevant issues in developing countries.

- Identify ways to improve the application of ethical principles in the conduct of research in varied cultural settings by 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.
- 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 an appropriate cultural context (including low literacy and local languages).
- Ensure that all research is conducted in accordance with international standards of human rights principles and respecting the dignity of persons.

Technology Transfer and Translation of Research Results

- Support operational research based on implementation science and innovative research designs not limited to randomized clinical trials (RCTs).
- Ensure research results are provided to, and understood by, participants and the community in which the study is conducted, as well as to the community's health professionals and personnel in relevant Ministries.
- Develop effective technologies 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 research results through enhanced information technology.
- Transfer clinical, laboratory, and public health technologies that may be sustained and used for implementation of prevention, symptoms management, clinical training, and patient care programs after research studies are completed.

OBJECTIVE–B: Mentoring and Training Investigators

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

STRATEGIES

- Provide sustainable research career development opportunities, with incentives for working in-country, for new, junior, mid-career, and senior investigators in resource-limited international settings.
- Provide opportunities for new, junior, mid-career, and senior investigators from both developed and developing countries to collaborate together on research projects in low- and middle-income countries and spend significant amounts of time working together in developing countries.
- 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 faculty and mentors for others.
- Continue to support research training, including degree training where appropriate, of clinicians and nonphysician professionals (such as nurses, midwives, and pharmacists), social and behavioral scientists, clinical pathologists, biostatisticians, public health professionals, and community health workers, and other researchers from developing nations to enhance the conduct of research on HIV/AIDS, other sexually transmitted infections (STIs), and HIV-related coinfections, malignancies, and comorbidities.
- Provide training in data collection, management, and analysis for in-country research personnel.
- Provide training in bioethics to strengthen in-country capacity for the ethical conduct of research, including application of informed consent, establishment of community advisory boards, and other topics related to the protection of human subjects.
- Support programs to develop and provide training in the responsible conduct of research in low- and middle-income countries.
- Develop and provide training at international sites conducting clinical trials on the role and responsibilities of an institutional biosafety committee.
- Enhance training in implementation science research (i.e., translational, operational, and health services research), including training in cost-effectiveness analysis to better respond to needed adaptation to local epidemics and local social and cultural issues.
- 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.
- Support research efforts to develop and assess the impact of novel training technologies with applications in low-resource settings, such as Web-based and distance learning, video conferencing, hand-held platforms, and other innovative training tools.
- Identify barriers that international investigators encounter in the NIH application submission process through www.grants.gov, and work with relevant agencies to address the barriers that prevent application submissions.

OBJECTIVE–C: Interventions to Alleviate Stigma and Discrimination

Develop and test interventions that address the issues of sex/gender, age, power relationships, stigma, and discrimination.

STRATEGIES

- Design and evaluate culturally appropriate strategies to reduce stigma and discrimination and increase willingness of individuals to enter into voluntary counseling and testing (VCT); identify and implement alternative infant-feeding practices; receive and adhere to ART and anti-tuberculosis (TB) drug regimens; and participate in HIV/AIDS research studies.
- Support the training of community leaders to become role models in the implementation of such strategies and interventions.
- Study age-, sex-, and gender-related social, behavioral, and biological factors affecting susceptibility to HIV infection and its acquisition or transmission, including intimate partner violence, the conflicting demands of childbearing, and avoidance of disease.
- 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.
- Conduct research on sex/gender identity and age differences and their impact on inequities in access to and use of resources, prevention and care services, and adherence issues, particularly in settings where rights of minorities or vulnerable populations are limited and/or where stigma persists.
- Evaluate the relationship between new technologies, structural interventions (e.g., male circumcision), and gender and power relationships.
- Encourage analysis of sex/gender and age differences in all relevant HIV-related research.
- Study how HIV infection psychologically affects women, including their role as heads of households and/or caregivers, their reproductive health requirements, and family support.
- Evaluate strategies to reduce stigma related to choice of infant-feeding modality by HIV-infected women.
- Develop and strengthen innovative research methods, including measures and study designs, for investigating the impact of stigma and discrimination (and interventions to decrease stigma) on HIV prevention, care, and treatment-seeking behavior.
- Evaluate attitudes (e.g., stigma) of health care providers regarding HIV-infected individuals and the effect of these attitudes on provision of care and treatment.
- Study how stigmatization within small social networks (e.g., ostracism and interpersonal violence) can be minimized in order to increase utilization of counseling, testing, and ART, and to reduce further transmission.

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

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

STRATEGIES

- Develop and test sustainable interventions at multiple levels (e.g., individual, couple, group, and society) that address multiple risk factors of HIV acquisition and transmission, targeting both HIV-infected and -uninfected individuals in specific populations and reflecting regional aspects of the epidemic.
- Define sexual and substance use behaviors and their predictors in HIV-infected populations, and design and test interventions to reduce the risk of HIV transmission.
- Study risk behaviors and prevention of such behaviors among individuals with perinatally acquired HIV who are surviving into adolescence and young adulthood.
- Study the movement of the HIV epidemic across borders and regions, and evaluate the effects of various policies and structural interventions related to migration and immigration on HIV transmission.
- Identify the most effective strategies to reach and prevent HIV transmission among mobile or at-risk populations.
- Develop analytical tools and support innovative methodologies, including ethnographic studies, to better understand and evaluate risk behaviors within social networks.
- Investigate the role of mental health conditions (e.g., depression) and use of psychoactive substances in promoting or facilitating high-risk sexual behaviors that reduce the efficacy of prevention strategies.
- Determine the factors involved in high-risk social networks (e.g., drug and alcohol users and individuals with physical and/or mental disabilities) that influence the rates and patterns of HIV infection, and design and test prevention strategies based on these results.
- Encourage molecular epidemiology studies of viral diversity in the context of social networks.
- Investigate the processes through which some social network interventions become self-sustaining forces for risk reduction and the frequency of this occurrence.
- Devise strategies to prevent substance use initiation, dependence, and transition to riskier drug practices, such as initiating drug injection and sharing injection equipment.
- Develop and test strategies specifically targeted to preventing transmission in serodiscordant couples.

OBJECTIVE–E: Structural Interventions

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

STRATEGIES

- Assess and determine optimal methodologies for evaluation of various structural interventions and their impact, encouraging the use of innovative study designs not limited to RCTs.
- Determine barriers and facilitators to acceptance of VCT, and develop more comprehensive and integrated health system-level approaches to the provision of VCT, including:
 - ▶ assessing new VCT approaches for effectiveness and cost-effectiveness with regard to reducing risk from sexual behaviors and substance use in settings with varying levels of HIV seroprevalence;
 - ▶ assessing approaches to integrate VCT into other existing health services, including TB and STI clinics, family planning, maternal and child health care, and child immunization services;
 - ▶ changing community norms for seeking VCT that encourage knowledge of one's status, help mitigate social harm, and reduce HIV stigma; and
 - ▶ developing and testing strategies for encouraging voluntary and safe partner notification within the context of families and couples counseling.
- 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, in particular:
 - ▶ identify the most effective and sustainable strategies for schools, leisure locations, and worksites to support behavior change interventions; and
 - ▶ examine structural interventions for HIV, STI, and TB prevention, treatment, and care among incarcerated populations.
- Conduct empirical data analysis and modeling to determine required coverage levels for different interventions in order to attain basic efficiencies and maximal effectiveness targeted to specific populations, including drug users and other at-risk groups.
- Evaluate the various approaches used by different countries for implementing structural interventions and investigate how these approaches may be systematically facilitated.

OBJECTIVE–F: Prevention Approaches

Design and evaluate the integrated application of effective and sustainable prevention tools and approaches in combination and at multiple levels, including synergistic biomedical, behavioral, and structural strategies, targeted to specific settings and populations at risk.

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, including infants born to HIV-infected mothers receiving antiretroviral (ARV) drugs during pregnancy or breastfeeding, for treatment or prevention of mother-to-child transmission (PMTCT).
- Develop and evaluate methods for increasing access to, acceptability of, and adherence to biomedical interventions, including ARV-based prevention, such as pre-exposure prophylaxis or treatment as prevention.
- Study and evaluate products that require minimal adherence, such as patches, vaginal rings, or longer-acting ARVs.
- Study and integrate the behavioral aspects of complex, combined biomedical interventions and strategies.
- Assess optimal combinations of existing prevention interventions for specific populations at high risk, as no single intervention is likely to eliminate HIV transmission in all groups.
- Examine novel study designs to evaluate the synergistic effects of combination prevention approaches, which permit attribution to specific components of the regimen.
- Conduct research on how best to deliver prevention education in the care and treatment setting, targeting interventions to both HIV-uninfected and -infected individuals.
- Conduct research to better understand coverage of available prevention interventions and barriers to their access.

Male Circumcision

- Determine the effectiveness, sustainability, and durability of male circumcision in reducing HIV transmission risk from men to women and men to men.
- Develop and evaluate innovative strategies for the safe and effective delivery of male circumcision and other male-oriented prevention services to prevent or reduce HIV transmission.
- Study the sociocultural aspects and other factors that may inhibit or encourage the use of male circumcision or affect its acceptability.
- Study the technical training and implementation requirements for widespread uptake of male circumcision interventions.
- Determine the cost-effectiveness of male circumcision in limiting transmission and curtailing the expansion of the epidemic.
- Evaluate whether circumcision is associated with behavioral disinhibition.
- Examine methods to increase uptake and demand for this service and evaluate best methods for scale-up, such as mobile clinics, task shifting, and others.
- Evaluate the effectiveness and consequences of expanded access to male circumcision programs.

Antiretroviral Use

- Determine the effectiveness of pre- and postexposure ARV prophylaxis in the prevention of sexual and blood-borne HIV transmission, while continuing to study and monitor drug resistance.
- Determine the most effective ARV agents, formulations, or combinations of agents to reduce transmission risk.
- Conduct research on ARV optimization in genital secretions and in the anorectal, oropharyngeal, and gut mucosa.
- Determine the social, cultural, and practical factors affecting the provision of ARV-based prophylaxis and/or understanding the barriers to implementation of pre- and postexposure prophylaxis.
- Examine strategies to increase long-term adherence and examine product formulations that do not require daily adherence.

Oral and Topical Microbicides and Barrier Methods

- Discover and develop candidate oral and topical microbicides and other physical/chemical barrier methods (particularly female-controlled methods) to prevent sexual HIV transmission, and identify barriers to long-term adherence.
- Conduct Phase I, Phase II, and Phase III clinical trials of suitable candidate oral and topical microbicides (including ARVs) in various international settings and in diverse populations, including pregnant women, for safety and efficacy.
- Develop appropriate biological and surrogate markers of safety or protection.
- Study the sociocultural and behavioral concerns related to partner involvement and acceptance of microbicide use, or covert use in the absence of partner willingness or acceptance.

- Determine the cost-effectiveness of microbicides and other physical/chemical barrier methods in limiting transmission and curtailing the expansion of the epidemic.

HIV Vaccine Development

- Continue accelerated efforts toward the development of HIV vaccine candidates suitable for use around the world, and foster the development of vaccines to optimize characteristics appropriate for broad international use, including low cost, ease of production and administration, and 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 (HIV incidence, viral subtypes, major histocompatibility types, and natural history) to guide decisionmaking regarding identification of potential international clinical trial sites and the conduct of vaccine clinical trials in these sites according to the highest clinical and ethical standards.
- Identify suitable populations of adults, adolescents, and children to enroll in clinical trials of candidate vaccines, while ensuring equitable and appropriately representative gender balance in enrollment.
- Conduct Phase I, Phase II, and Phase III clinical trials of suitable HIV candidate vaccines in diverse international settings for safety, immunogenicity, and efficacy, with appropriate surrogate markers and measures of correlates of protection.
- Enlist the participation of local community representatives in the development of appropriate clinical 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 HIV vaccine research and its acceptability in diverse populations.
- Conduct research on the potential social and economic effects, including cost-effectiveness, of the use of HIV vaccines.

Sexually Transmitted Infections 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 human papillomavirus (HPV).
- Identify gender-related biological factors affecting susceptibility to HIV infection, including the use of hormonal contraceptives and the presence of gender-specific conditions such as HPV infection, cervical cancer, and genital ulcer disease.
- Examine how coinfection with other endemic diseases affects HIV transmission, acquisition, and disease progression.
- Determine the role of sexually transmitted coinfections and opportunistic infections on HIV transmission, acquisition, and disease progression.

Substance Abuse

- Develop and evaluate innovative, culturally relevant, and contextually appropriate alcohol and drug abuse treatment programs for their utility as HIV and hepatitis C virus (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 approaches to integrate risk-reduction prevention strategies for drug and alcohol use into HIV treatment and primary care settings.
- Develop and evaluate innovative strategies for identifying “hidden populations” of young, older, and out-of-treatment drug users, including those in high-income social strata and in developing countries.

Mother-to-Child Transmission: Considerations for the Mother, Child, Adolescent, and Family

- Develop and evaluate strategies:
 - ▶ for primary prevention, i.e., prevention of HIV acquisition by adolescent girls and women;
 - ▶ to evaluate reproductive decisionmaking and improve reproductive health in serodiscordant couples, including HIV-risk reduction during *in vitro* fertilization; and
 - ▶ for prevention of unintended pregnancy by HIV-infected adolescent girls and women, and study factors associated with unintended pregnancy.
- Investigate the mechanisms of and risk factors for *in utero*, intrapartum, and postnatal mother-to-child transmission (MTCT) of HIV.
- Develop new, effective, safe, and feasible strategies to further decrease vertical transmission of HIV, particularly postnatal (breast milk) transmission, or provide alternatives to currently identified effective strategies.
- Further evaluate and adapt known efficacious interventions in infants, mothers, or both to prevent MTCT (i.e., ARV prophylaxis, cesarean section before labor and before ruptured membranes, complete avoidance of breastfeeding, exclusive breastfeeding, and ARV prophylaxis to breastfeeding infants and/or lactating mothers).
- Evaluate the effects of perinatally acquired HIV infection in adolescent girls who become pregnant and receive treatment regimens to prevent MTCT.

- Evaluate acquisition of HIV infection during pregnancy:
 - ▶ quantify more precisely the risk of MTCT when maternal HIV infection is acquired during pregnancy; and
 - ▶ develop strategies for detecting or reducing maternal incident infection during pregnancy.
- Investigate the unique immune status of pregnant women and their infants and develop passive and active immunization interventions to interrupt HIV transmission.
- Evaluate risk factors and strategies to reduce the morbidity and mortality associated with HIV infection in pregnant and postpartum women and their HIV-exposed infants, including:
 - ▶ maternal and infant nutrition during the peripartum and postpartum periods; and
 - ▶ the association of maternal HIV disease stage and mortality of both HIV-infected and -uninfected children.
- Investigate the effect of ARV regimens used for prevention of MTCT, including repeated interventions, on subsequent response to ARV used for treatment in mothers and infants, if infected despite prophylaxis.
- Conduct implementation science research on identifying barriers to developing effective strategies for scale-up and delivery of successful interventions for prevention of MTCT of HIV, in view of the new World Health Organization (WHO) recommendations on prevention of MTCT and infant feeding.
- Conduct implementation science research focused on the cascade of steps for prevention of MTCT beginning at prenatal care and extending to adherence at delivery, and examine ways to prevent loss to followup at any point.
- Evaluate strategies to ensure linkage of sites (and data from sites) conducting prevention of MTCT with sites providing maternal ART treatment and with pediatric health clinics.

OBJECTIVE–G: Optimal Use of Antiretroviral Treatment and Other Interventions for HIV Epidemic Control

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

STRATEGIES

- Develop and test region-specific strategies to support adherence to medication regimens in adults, adolescents (including those who acquired HIV through perinatal transmission), and children, to enhance therapeutic outcomes and limit the development of drug resistance, in particular:
 - ▶ promote treatment literacy for health care workers, people living with HIV/AIDS, and family and community members;
 - ▶ evaluate the effectiveness of different approaches to task shifting for HIV care and treatment from physicians to nonphysician staff;
 - ▶ determine the role of pharmacogenetics/pharmacokinetics and identify appropriate ARVs that can be used in specific populations throughout the life course;
 - ▶ develop appropriate pharmacovigilance systems to evaluate short- and long-term effects of treatments provided to HIV-infected individuals (including special populations such as pregnant women and alcohol or substance users); and
 - ▶ examine the effectiveness of a variety of approaches to the administration of therapy (e.g., directly observed therapy, directly delivered therapy, or directly administered ART) and provision of care to targeted groups, such as health care workers, security forces, and teachers.
- Develop and evaluate public health models, such as family and community models of care that integrate HIV/AIDS care and other existing health services for infants to older adults in a single setting to maximize outcomes and avoid duplication of effort, including:
 - ▶ evaluating and monitoring treatment effectiveness, adherence, drug-drug interactions, drug resistance, and toxicity of ARVs and prophylaxis medications against major coinfections and opportunistic infections in pediatric, adolescent, and adult populations (including over age 50 and pregnant women) in resource-constrained settings; and
 - ▶ developing and evaluating the use of HIV treatment as a component of prevention interventions.
- Assess the cost-effectiveness of ARVs in resource-limited settings, in particular:
 - ▶ identify affordable, safe, and effective ARV regimens, including timing of initiation and durability of initial treatment;
 - ▶ 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) and validate low-cost monitoring technology; and
 - ▶ determine the minimal level and methods of targeted drug-resistance monitoring necessary in those failing therapy and pregnant women.

- Conduct research on biological, behavioral, and psychosocial effects related to the diagnosis, treatment, and care of HIV disease among children and adolescents (both horizontally and perinatally infected), in particular:
 - ▶ develop and evaluate suitable and sustainable approaches for the diagnosis of HIV infection, especially for children under the age of 18 months; and
 - ▶ support the long-term followup of children exposed to ART *in utero* and/or postpartum in resource-limited settings to evaluate possible late effects of ARV exposure.
- Characterize the clinical course of HIV infection in diverse geographic settings and determine the efficacy of ARV regimens on various clades prevalent around the world.
- Assess the effect of nutritional status and nutritional interventions on patient survival and the efficacy and tolerability of ART, including measuring the rate of immune system deterioration.
- Conduct community-based studies that assess the effect of community mobilization on VCT and treatment success.
- Develop, evaluate, and implement programs to prevent discrimination in the provision of ARV treatment, and determine whether expanded ART care leads to a decrease in HIV-associated stigma.
- Collaborate with clinicians from resource-limited countries to identify, recruit, and retain individuals with acute and early HIV infection in treatment research programs.
- Conduct basic research on latency and eradication of viral reservoirs that could lead toward a functional or actual cure of HIV.

OBJECTIVE–H: Integrated Prevention and Treatment

Evaluate the impact of prevention and treatment programs on the HIV epidemic, including the integration of comprehensive prevention and clinical care related to HIV/AIDS into existing health service delivery programs.

STRATEGIES

- Develop effective strategies for and evaluate the integration of the delivery of HIV care with primary care and other medical and social services, while enhancing and optimizing linkages among interdependent programs, such as those for control and management of TB and other comorbid conditions, alcohol/substance abuse or dependence treatment programs, maternal and child health services and family planning, and support services for the elderly, in particular:
 - ▶ determine how availability of ART affects utilization of VCT and entry into care and treatment in various communities;
 - ▶ determine how availability of ARV prophylaxis for prevention of MTCT affects entry into antenatal care (ANC) and utilization of VCT within ANC;
 - ▶ examine novel strategies to increase uptake of routine HIV testing;
 - ▶ examine the potential use of HIV therapeutic vaccines;
 - ▶ develop and test optimal strategies to integrate ART treatment programs with region- and/or country-specific cancer services for diagnosis and management of HIV-associated malignancies to allow a continuum of care and enhanced outcomes of comprehensive HIV care; and
 - ▶ develop strategies to control the HIV epidemic and strengthen existing infrastructure that simultaneously address multiple health outcomes.
- Assess the biological, social, psychological, societal, and economic impacts of ART on risk behaviors, HIV transmission, and prevalence, including associated behavior change, in individuals across the lifespan, families, and various communities, in particular:
 - ▶ study the direct effects of ART on HIV transmission, e.g., by evaluating the effectiveness of specific ART strategies in curtailing HIV transmission in HIV-serodiscordant couples;
 - ▶ evaluate the interactions of ARVs with alcohol, psychoactive drugs, traditional medicines, or medications used for the treatment of substance abuse, and investigate the effects of these comorbid conditions (and their integrated treatment) on HIV disease progression, adherence to treatment regimens, and clinical outcomes;
 - ▶ consider the implications of ART use for prevention in settings where ART is not available for all those infected individuals who meet WHO eligibility criteria; and
 - ▶ determine how ART affects breastfeeding behaviors.
- Examine innovative ways to measure HIV incidence at a community level.
- Develop biomarkers that can serve as surrogates for measurement of HIV-risk behaviors and can be used to predict and monitor rapid escalation of HIV subepidemics (i.e., in local areas or in high-risk groups).

- 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, in particular:
 - ▶ develop demonstration programs that simultaneously address prevention, care, and treatment;
 - ▶ prior to the scale-up of HIV prevention, care, and treatment programs in a limited-resource context, determine how limited resources can best be utilized to attain required coverage levels;
 - ▶ evaluate the impact of scale-up of HIV prevention, care, and treatment programs at a population level to determine the most opportune time for evaluation of national-level interventions; and
 - ▶ ensure that implementation research is adapted to address the local epidemic.
- 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.

OBJECTIVE–I: Endemic Diseases, Comorbidities, and HIV

Study the interactions between HIV infection, endemic diseases, and the entire spectrum of comorbidities (including alcohol and substance use, psychiatric illness, and other organ system disorders), with a particular focus on diseases that affect HIV care, and develop strategies to optimize their integrated prevention, diagnosis, treatment, and care.

STRATEGIES

- 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 and urologic diseases; musculoskeletal and skin disorders; and neurological and neuropsychiatric conditions) in adult, adolescent, and pediatric populations specific to individual regions in diverse geographic settings.
- Identify and study conditions that emerge as a consequence of ART and longer survival, such as malignancies, neurological and neuropsychological conditions, and metabolic and nutritional dysfunctions.
- Investigate sustainable strategies for preventing, treating, and monitoring responses to treatment of endemic diseases in HIV-infected adults, adolescents, children, and infants in resource-constrained settings.
- Identify comorbidities in HIV-exposed, uninfected infants and young children, using appropriate control populations, in resource-constrained settings.
- Investigate operational strategies for responding to the converging epidemics of HIV, TB, alcohol and substance abuse, and other comorbidities, while considering issues relevant to long-term treatment specific to the regional epidemic.
- Develop simple clinical algorithms for guiding initiation of prevention or treatment of HIV-related coinfections, OIs, malignancies, and other comorbidities.
- Identify affordable strategies to target high-risk patients for initiation of prophylaxis for HIV-related coinfections, OIs, and comorbidities.
- Develop and test new, low-cost, effective, and rapid diagnostic tools and drug susceptibility tests for comorbid diseases and conditions, including TB, malaria, and early precancerous lesions.
- Examine the role of coinfections 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 effect of ART on susceptibility to infection with endemic diseases, and on their natural history.
- Determine the effect 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.
- Study the association between HIV, aging, and the development of AIDS-related comorbidities throughout the lifespan.
- Assess the burden of TB and the relative importance of reactivation versus *de novo* infection in HIV-coinfected individuals in various settings.
- Develop and study strategies for primary and secondary TB prevention, including prophylactic regimens in HIV-infected patients.
- Develop and study feasible and effective strategies for prevention of transmission of drug-susceptible and drug-resistant TB in community and health care settings.

- Determine optimal ways of integrating treatment of HIV disease with prevention and treatment of OIs, endemic diseases, and comorbidities, especially TB, including clinical research to assess clinical outcomes and operational research to determine cost-effectiveness.
- Determine the safest and most efficient treatment modalities for endemic diseases (e.g., TB, HCV, HIV-associated cancers, and malaria) in HIV-infected adult, pediatric, and adolescent populations, including pregnant women.
- 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 in HIV-infected adult, pediatric, and adolescent populations, including pregnant women.
- Develop new agents and therapeutic strategies to treat drug-sensitive and drug-resistant TB (including multi-drug-resistant [MDR]-TB and extensively drug-resistant [XDR]-TB).
- Investigate behavioral and cultural factors related to endemic coinfections, within the context of HIV, and develop strategies to enhance and monitor adherence to therapy and prophylaxis for endemic coinfections in HIV-infected individuals.
- Develop methods to monitor the development of resistance to ARV and anti-TB drugs in clinical study participants.
- Determine the safety and effectiveness of available immunizations for endemic pathogens in diverse HIV-infected populations.
- Conduct studies to better understand the role and mechanism of reinfection and/or superinfection with HCV in coinfecting individuals.
- Develop and test the feasibility of low-cost assays for early diagnosis of viral cancers, particularly oral and cervical cancer, non-Hodgkin's lymphoma, and Kaposi's sarcoma, and utilize these to develop adequate clinical approaches to the management of such cancers in regional settings.

AREA OF EMPHASIS

Training, Infrastructure, and Capacity Building

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE–A: Research Training

Provide training in biomedical, social and behavioral, and intervention research on HIV and its associated complications, coinfections, and comorbidities, with an emphasis on multidisciplinary research in populations that are diverse with respect to gender, race, and culture, including marginalized populations domestically and internationally, particularly in countries with high HIV incidence and/or high prevalence of HIV infection.

STRATEGIES

- Increase opportunities for prebaccalaureate, undergraduate, predoctoral, doctoral, postdoctoral, and advanced research training across a broad range of AIDS-related scientific disciplines, and support research to better understand the barriers and incentives along the research career pathways for investigators.
- Enhance programs that improve recruiting, training, mentoring, and retaining investigators—especially those from diverse scientific backgrounds, including biomedical, behavioral, and social scientists—in AIDS research.
- Increase opportunities for highly trained specialists to develop skills in AIDS research, such as, but not limited to:
 - ▶ Opportunities for pediatricians, adolescent medicine specialists, and geriatricians in HIV prevention, diagnosis, manifestations, complications, and treatment.
 - ▶ Opportunities for HIV prevention researchers interested in adding specific methodological skills to their research expertise.
 - ▶ Opportunities for related specialists such as pharmacologists and dental scientists to develop skills in AIDS research.
 - ▶ Opportunities for veterinarian scientists conducting AIDS research using animal models, including nonhuman primates (NHPs).
- Implement new research training programs for non-physician professionals—such as physician assistants, nurse practitioners, and laboratory staff—in resource-limited settings and at domestic sites to increase the diversity of the pool of AIDS researchers.
- Support and expand training programs for basic and clinical/applied researchers across disciplines:
 - ▶ Provide training and promote standardized certification in Good Laboratory Practice/Good Clinical Practice for staff in domestic and international settings where clinical research on AIDS is being conducted.

- ▶ Expand the capacity for basic and clinical/ applied research on HIV and HIV-related complications, coinfections, and comorbidities (e.g., tuberculosis, hepatitis, cancers, and antiretroviral therapy [ART]-related complications such as cardiovascular and metabolic consequences) in the United States and in resource-limited countries.
- ▶ Support training programs for personnel in institutions in resource-limited settings to strengthen the administrative and financial management capacity needed to conduct HIV-related research, as well as to integrate best practices and applicable research results into program planning and implementation.
- ▶ Expand programs that provide support for international AIDS researchers trained in NIH-sponsored programs to continue their research in their home countries.
- ▶ Expand programs that utilize the infrastructure at NIH-sponsored AIDS clinical trial sites for training programs in the design and conduct of clinical research.
- Support training opportunities for tested and emerging research methodologies relevant to HIV such as methods to conduct cost-effectiveness analyses, measurement of biologic outcomes in behavioral intervention studies, appropriate use of behavioral and social science measures in clinical trials, ethnographic and other qualitative methods, and network/systems analysis.
- Expand the NIH AIDS Loan Repayment Program to encourage promising U.S. scientists and physicians to pursue HIV-related research careers, placing an emphasis on those from disadvantaged backgrounds and/or from racial and ethnic minority populations.
- Establish mentoring networks to improve the supply of trained mentors for the development and retention of new investigators in all aspects of AIDS research, and support research that develops an evidence-based approach to effective mentoring so that future mentoring programs can build on best practices and the knowledge base of educational and social science research.
- Strengthen cultural competency training and ethics training for the conduct of AIDS research in vulnerable populations, in both domestic and international settings.
- Develop research training programs in the area of blood safety to develop improved blood screening strategies and technologies and appropriate use of transfusions.
- Develop new models of integrated training and mentoring that focus on the protection of human and animal subjects in AIDS research.
- Support the development and sharing of novel techniques from relevant research fields to the HIV/AIDS field, including structural biology, computational biology, genomics, metabolomics, proteomics, and systems science to understand HIV/AIDS-associated disorders. Encourage and facilitate collaborative and interdisciplinary research in these areas.
- Support development and analysis of distance learning used to teach research and research-related topics as well as to assess and better understand the acquisition of research skills and competency.

OBJECTIVE–B: Infrastructure and Capacity-Building Development

Establish and maintain the appropriate infrastructure and capacity needed to conduct AIDS research domestically and internationally, with emphasis on populations of high prevalence.

STRATEGIES

- Enhance and improve research capacity and infrastructure to advance research on HIV and HIV-associated coinfections, comorbidities, and other complications.
- Enhance and improve the infrastructure to conduct clinical trials of prevention and therapeutic strategies in domestic and international sites, including laboratory capacity, trained scientists and other personnel in appropriate numbers, appropriate participant cohorts, and establishment of local institutional review boards to address bioethical issues.
- Support the infrastructure necessary for producing AIDS vaccine candidates under Good Manufacturing Practices for preventive and therapeutic vaccine clinical trials.
- Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing AIDS epidemics, and maintain updated databases, allowing their broader and more efficient use by the scientific community, when appropriate.
- Establish and support quality-controlled repositories, biobanks, and well-characterized panels of reagents to ensure access by qualified scientists to human blood and tissue specimens from clinical trials and cohorts. Improve and disseminate the process of requesting, prioritizing, and receiving these specimens to allow timely and equitable access.
- Develop, validate, and utilize experimental animal models, *ex vivo*, and theoretical/mathematical models to study the transmission and establishment of HIV/SIV/SHIV (chimeric simian/human immunodeficiency virus) infections, with emphasis on models of direct relevance to human HIV infection and models that address important issues not readily approachable in human subjects.
- Promote Internet connections, cell-phone-based communication, and online social networks, including those with virtual worlds for training, infrastructure, and treatment, taking into consideration appropriate levels of confidentiality/security. Ensure availability of pertinent and secure information technology at health science centers, hospitals, outpatient clinics, community-based organizations (CBOs), and other access points, both domestically and internationally, for HIV-related research and patient care.
- Develop statistical sampling methodologies, data collection protocols, and statistical analysis tools that are easy to use and adaptable to different settings; and facilitate efficient statistical analysis and enhance report generation and standardization when appropriate in the context of AIDS research.
- Promote research in, and application of, medical informatics (e.g., high-performance computing) for AIDS research and clinical practice in resource-limited settings, both domestically and internationally.
- Develop efficient and effective systems for collecting and managing HIV/SIV/SHIV multiple-center and single-site clinical and animal model trial data, and ensure timely and accurate dissemination of clinical and animal model trial information.
- Increase collaborations between CBOs/nongovernmental organizations and other Government-supported health care service providers and academic researchers to improve the quality and capacity of AIDS research in health care service settings.

Domestic

- Support enhanced research infrastructure at U.S. minority-serving institutions to improve capacity to support AIDS research.
- Support AIDS research planning and organizational initiatives targeting domestic minority institutions and minority-serving communities with emphasis on initiatives that develop academic–community partnerships.
- Expand opportunities for institutions serving specific diverse populations at risk for HIV to develop equal and productive partnerships with U.S. institutions serving primarily broad-based, majority populations.
- Develop programs to sustain human capacity and to link U.S. AIDS research scientists, industry partners, and relevant institutions with each other and with investigators and institutions in both resource-developed and -developing countries.
- Develop strategies to promote the infrastructure for bidirectional translational science by enhancing national capacity for clinical and translational AIDS research, supporting team-building and consortium collaborations, and facilitating the use of national data-sharing HIV networks.
- Support and expand adequate facilities and resources, including BSL-2/3 (Bio Safety Level 2/3) facilities for studies in NHPs, and provide appropriate ethical and procedural training to house and breed NHPs for use in AIDS research.
- Expand the breeding of genetically defined specific pathogen-free NHPs, with emphasis on Indian-origin rhesus macaques.
- Develop and characterize appropriate reagents for use in HIV-related research conducted in different species of macaques and other NHPs.
- Support programs that enhance the current AIDS research infrastructure, such as the Centers for AIDS Research, the Clinical and Translational Science Awards Consortium, the Research Facilities Improvement Program, and the National Primate Research Centers.

- Support the Biomedical Technology Research Centers Program for structural studies on HIV proteins and host proteins.

International

- Enhance and improve research infrastructure and capacity in resource-limited settings with high HIV incidence, with particular emphasis on facilities for research on HIV prevention, therapeutics, and behavioral interventions.
- Enhance coordination and collaboration among NIH-supported investigators, other U.S. Government agencies, and other international agencies conducting AIDS research in the same countries.
- Enhance opportunities to evaluate successful HIV prevention and therapeutic strategies in resource-limited countries that also could be used in the United States.
- Develop and improve conventional and electronic systems for documentation of medical care and tracking of HIV infection and AIDS in low-resource settings to improve epidemiologic research.
- Increase population-based cancer registration in resource-limited countries to allow for a better understanding of cancer rates in HIV-infected persons in these locations.

