

NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2005

PLAN FOR HIV-RELATED RESEARCH

VI: MICROBICIDES

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Microbicides

SCIENTIFIC ISSUES

There is a real need and urgency to expand the range of interventions for preventing HIV transmission. It is not known when a safe and effective vaccine will be developed, and even when such a vaccine will become available, it is acknowledged that a vaccine will be only one of the many approaches to preventing HIV infection. In the interim, nonvaccine prevention methods are needed that can be controlled by women to prevent HIV transmission. Microbicides, defined as antimicrobial products that can be applied topically for the prevention of sexually transmitted infections (STIs), including HIV, may offer one of the most promising preventive interventions that could be safe, effective, inexpensive, readily available, and widely acceptable. Microbicides used alone or in combination with physical barriers could be used both by HIV-infected individuals to prevent transmission to their partners and by uninfected individuals to protect themselves from acquiring HIV. Furthermore, microbicides could also be used as a mode of protection by men who have sex with men. Thus, a consensus has emerged across the STI and AIDS research communities that development of microbicides presents an important opportunity and challenge that stands in need of greater investment.

The impact of AIDS on developing nations of Africa, Asia, Latin America, the Caribbean, and the former Soviet Union countries is staggering, with even greater numbers of projected new infections to come. In these countries, heterosexual transmission is the predominant mode of HIV spread. Recent data indicate that worldwide there are now almost equal

numbers of men and women infected with HIV. In sub-Saharan Africa, the area hardest hit by the pandemic, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimated that 17.6 million women were living with HIV/AIDS at the end of 2000, nearly equal to the number of HIV-infected men. Of the more than 16,000 estimated new infections every day, half occur in young persons between the ages of 15 and 24, and teenage girls are disproportionately affected compared to boys. Attitudes, beliefs, and taboos surrounding sex, the status of women and children, and the source and etiology of AIDS also complicate attempts to control transmission and provide appropriate prevention and treatment.

In the United States, the HIV/AIDS epidemic continues to evolve. Although the incidence of new AIDS cases has declined, attributed largely to expanded use of new antiretroviral therapies (ART), the decline in death rates observed in the late 1990s has leveled off. Further, according to the Centers for Disease Control and Prevention (CDC), the rate of new HIV infections has been constant, indicating that the overall epidemic is continuing to expand. In fact, HIV infection rates are continuing to climb in a number of subpopulation groups, including women, racial and ethnic minorities, young homosexual men, and people more than 50 years of age. These data forebode an epidemic of even greater magnitude in the coming years. In the United States, more than 30 percent of newly reported HIV cases diagnosed are occurring in women, according to the most recent data collected by the CDC.

As in the rest of the world, the majority of these reported HIV infections among U.S. women result from heterosexual transmission, and the data suggest that younger women are disproportionately at risk for acquiring HIV.

The number of new infections worldwide shows that, although consistent and correct use of condoms can provide excellent protection against HIV transmission, for a number of different reasons, men are reluctant to use condoms and women may also be reluctant to ask for their use. Prevention options under women's direct control to protect themselves from acquisition of HIV and STIs remain minimal. Prevention programs that promote condom use require a certain level of communication and negotiation between partners. But for many women in the United States, in other developed countries, as well as in developing countries, negotiating safer sex that includes the use of condoms may not be possible. Women, especially in developing countries, are economically, culturally, and socially marginalized. As a result, male/female power relations are not balanced, and women become infected because they cannot insist on condom use or

cannot protect themselves from nonconsensual, coercive sex. Further, the desire to achieve pregnancy is a deterrent to condom usage by many couples. Paradoxically, many women are infected during intercourse with their husbands, suggesting that microbicides are needed for use by women in their primary partnerships.

In response to this urgent need, the NIH AIDS prevention research agenda has made a high priority the development of barriers that can be applied topically intravaginally and intrarectally to inactivate or block HIV and other STIs. The NIH has a comprehensive research program that includes the screening, discovery, development, preclinical *in vitro* and *in vivo* testing, and clinical evaluation of compounds that have the potential to act as antimicrobial agents with both spermicidal and nonspermicidal activity, and social and behavioral studies to evaluate the possible acceptability of such agents. The NIH closely collaborates with academia and industry to identify and explore new and existing compounds as potential topical microbicidal agents.

Animal model testing and toxicity studies of potential lead compounds are conducted through NIH-sponsored contracts before these agents are considered for clinical trials. The NIH also supports Phase I, II, and III clinical trials of potential microbicides in both domestic and international settings. Currently four categories of compounds are undergoing thorough testing: cell/pathogen surface disruptive agents that kill or inactivate viruses and pathogens (benzalkonium chloride, chlorexidine, SDS, and C31G); inhibitors of viral binding and fusion/entry into susceptible cells (sulfated/sulfonated polymers, cyanovirin, and gp41 fusion inhibitors, RANTES analogs); enhancers of normal vaginal defense mechanisms (lactobacilli, acid buffers, peroxidases, antibiotic peptides, and monoclonal antibodies); and inhibitors of HIV replication (antiretroviral [ARV] drugs such as nucleoside and non-nucleoside reverse transcriptase inhibitors). Some of these products are nonspecific and have both spermicidal and antimicrobial activity against HIV and other pathogens, and some specifically interfere with HIV attachment and entry or the ability of the virus to replicate once it has entered a susceptible cell. Microbicides for HIV prevention would not need to be inherently spermicidal, but could be formulated with or without spermicidal activity.

The NIH AIDS prevention research agenda has also made the acceptability and use of microbicides among diverse populations a high priority within its portfolio of behavioral and social science research to ensure that these agents will be used by those at risk in order to halt the further sexual transmission of HIV and other STIs.

PRIORITY FOR FUTURE RESEARCH:

- **Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on microbicides discovery and development.**

In spite of the enormous potential of microbicides, there are no definitive data or proof of concept as yet establishing that any product applied topically in humans can prevent HIV infection. Although microbicides have been under development for more than a decade, there is a general perception that there has been insufficient progress in this area. Many factors may have contributed and continue to contribute to this lack of progress, including important scientific challenges presented by aspects of microbicides research and development.

One of the major challenges to progress is the requirement for a complex multidisciplinary and multisectoral approach by teams of scientists with expertise ranging from the biomedical to the behavioral and social sciences to experts in clinical trials and drug discovery and development. Since the field of microbicides is a relatively new specialization in prevention research, there are few acknowledged experts and a limited number of researchers working in the area. Therefore, there is an urgent need for more researchers to become involved in the field of microbicides. Research innovation and progress require a critical mass of both experienced and new investigators, many of whom have not traditionally engaged in research collaborations. More creative and innovative mechanisms should be created and implemented to attract new scientists to this research area since conventional funding mechanisms might not be the most appropriate.

PRIORITY FOR FUTURE RESEARCH:

- **Foster the development of varieties of endogenous and exogenous microbicial products that are based on specific biological and physiological pathways involving mucosal routes of HIV transmission.**

Basic biological and physiological research is of fundamental importance for the field of microbicides research. Translation of basic insights into HIV biology and pathogenesis, knowledge of the different steps required for HIV transmission and local propagation at mucosal surfaces, and a better understanding of immune responses in the reproductive tract are essential for identifying new targets for microbicides discovery and development. Early work has focused on nonspecific inhibitors of HIV. However, specific approaches hold the greatest promise for microbicides that would be effective at very low concentrations without interfering with normal cellular processes. Therefore, there is a clear need to increase our

understanding of the basic mechanisms and factors influencing HIV transmission at mucosal surfaces in order to identify multiple safe and effective strategies for blocking the early steps in the infectious process. Important areas of research include the identification of new viral and host targets for microbicide discovery, the determination of the first cell or tissue type that becomes infected and locally propagates HIV infection as well as the nature of the actual infectious unit, the elucidation of the impact of microbicides on regional immune responses, the development of studies of intercourse physiology, the elucidation of the mechanism by which inflammation and/or concomitant infections influence HIV transmission, and the investigations of the effects of endogenous and exogenous hormonal states on the susceptibility to infection. Emphasis should also be placed on studies of the normal vaginal and rectal ecology, since the ideal microbicide should not affect each ecosystem's integrity and balance. An understanding of the components of these ecosystems and their function, as well as the effect of microbicides use on these environments, is essential to the development of safe and effective topical microbicides.

PRIORITY FOR FUTURE RESEARCH:

- **Identify relevant practical and accessible methodologies to assess preclinical/clinical safety and activity of microbicides in a standardized fashion.**

An effective translation of basic insights into HIV biology and pathogenesis is also important for developing and validating relevant *in vitro* and *in vivo* models to assess safety and efficacy of candidate microbicides. This is an area of utmost importance since the preclinical evaluation of microbicidal products should support the rationale for clinical testing in humans by providing clear evidence of activity against HIV and other STIs in the absence of local and systemic toxicity. Because topical microbicides will be used predominately by HIV-uninfected individuals, the standards for safety of regular use are higher than for therapeutics where the risk/benefit ratio generally favors treatment. However, many of the methods for evaluating safety are borrowed from the drug development and the contraceptive fields and might not be either relevant or appropriate for testing microbicides. *In vitro* safety studies using tissue culture cell lines or human tissue explants are of uncertain clinical relevance, and we still do not have a good understanding of what are the most important indicators of safety in human studies. Efforts to standardize the most relevant methodologies so that the results from different studies can be compared would greatly accelerate progress in this field.

The lack of a well-established correlation between *in vitro*, animal models, and clinical testing; the insufficient knowledge about the biology of sexual transmission of HIV and other STI pathogens; the lack of optimal formulations; and the insufficient knowledge on cervicovaginal and intercourse physiology are posing formidable challenges to rapid progress in this field and should represent the target of intense investigations by NIH-sponsored researchers. It is also important to develop appropriate methods to assess anorectal safety of these products because of the potential use of effective products formulated for vaginal application to the rectal compartment.

PRIORITY FOR FUTURE RESEARCH:

- **Foster the development of combination approaches in acceptable formulations to prevent transmission and acquisition of HIV and other STIs, such as chemical and physical barriers, and microbicides with different specificities and mechanisms of action.**

Microbicides can be available alone or in combination with different agents within the same product or in combination with physical barriers, such as the female condom, the cervical cap, or the diaphragm. The potential higher susceptibility of the cervix to HIV infection may require the additional level of protection provided by a physical barrier. In addition, different active agents in the same products might act synergistically or sequentially against a single pathogen or expand the range of activity against other pathogens. The ideal microbicide needs to be effective against a range of sexually transmitted viruses and pathogens. This is of particular importance for HIV prevention efforts, since other STIs have been shown to promote the transmission of this virus. A broader range of microbicidal activity can be achieved by combining agents against other viruses or pathogens in a single product. For example, a combination of nonspecific inhibitors of viral attachment such as sulfated or sulfonated polymers with specific inhibitors of HIV entry may offer a specific chemical barrier against HIV, while also protecting against other types of infections.

PRIORITY FOR FUTURE RESEARCH:

- **Promote innovative methods to develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from multiple scientific disciplines.**

One of the most challenging steps in the development of safe, effective microbicides is combining the active microbicidal agents into vehicles, such as gels, creams, foaming tablets, suppositories, etc., that will enable delivery to the vagina or rectum and inactivation of infectious pathogens in the ejaculate

and cervical/vaginal or rectal compartments. Formulation expertise is essential at the earliest stages of drug development to ensure optimal performance characteristics and acceptance by a wide variety of users.

Vaginal spermicides and medications have been successfully formulated by the private sector and provide a framework in which to consider some of the characteristics of the formulated product. The ideal formulation should provide a uniform and durable protection at the mucosal sites without compromising the integrity of the mucosa, perturbing the local ecology, or having a systemic absorption. Formulations can have a major impact on microbicides' performance by either enhancing or decreasing the activity of the active agents. However, the interaction of formulation excipients on the active agents has been largely unexplored. The field of microbicides will clearly benefit by the development of formulations that, when used alone without active agents, would have no measurable impact on product performance and therefore could be used as inert placebos in clinical trials.

The science of rectal and vaginal formulations is very complex, drawing knowledge and expertise from multiple disciplines and sectors, and is a critical component of the effort to develop safe and effective microbicides.

PRIORITY FOR FUTURE RESEARCH:

- **Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase II/III microbicides clinical trials.**

After preclinical evaluation, the most promising candidate microbicides should be clinically evaluated in humans for safety and effectiveness. Safety studies (Phase I/II) are necessary to evaluate the potential for systemic absorption and toxicity as well as local toxic effects such as irritation, ulceration, itching, and burning. Irritation and ulceration of the vaginal, cervical, penile, or rectal epithelium might compromise the integrity of mucosal tissue at those sites with a concomitant increase in the risk of HIV and STI pathogen transmission. Moreover, all adverse effects have a negative impact on the acceptability of microbicides and influence the future use of these products.

Efficacy/effectiveness studies (Phase III) are then needed to assess the ability of these products to prevent HIV and/or HIV infection, depending upon the product indication. Microbicide trials are more complex than vaccine trials in that they require huge and complex efficacy and effectiveness studies that must be conducted in areas with high HIV incidence rates; such rates occur predominantly in developing countries with minimal

research infrastructure resources. The ethical obligation to provide behavioral counseling and availability of condoms to the study subjects adds to the complexity and size of the trials. The first Phase III clinical studies of candidate microbicides have raised problematic issues that have prompted a re-evaluation of timing and methodologies for microbicides clinical trials. Several ways of streamlining this phase of development are now under consideration, including running parallel studies on a given product and testing multiple products in a single trial. Other important areas of research include the establishment of clinical trial sites and the necessary clinical, laboratory, and data management infrastructure to conduct those trials, especially in developing countries; the development of criteria for selecting products to be evaluated in clinical trials and for moving them through the different phases of those studies; and research into ethical and behavioral issues impacting HIV prevention clinical trials. Training is an essential component of building the appropriate infrastructure to conduct clinical studies in developing countries as well as the involvement of communities in the planning and undertaking of international microbicide research. Emphasis should be placed on the development of local institutional review boards (IRBs) and community advisory boards.

Work with national and international regulatory bodies to address regulatory issues should proceed in parallel, in order to promote the rapid development of microbicides. Collaboration with industry, as well as Government and nongovernment organizations and foundations, should be encouraged. At the same time, it must also be ensured that clinical studies of microbicides are undertaken with high ethical standards.

PRIORITY FOR FUTURE RESEARCH:

- **Conduct social and behavioral research in concert with microbicides clinical trials, including research on product use, sexual behaviors, and the identification of reliable and valid behavioral measures for use in trials.**

The effectiveness of any microbicide will depend upon its adoption and continued use by individuals and couples. Social and behavioral research on how the choice, acceptability, and use of microbicides affect and are affected by a variety of social, psychological, and cultural factors (including differences in human sexuality) is an essential element of preclinical and clinical studies. To date, little is known about how people can and might incorporate the use of microbicides into their sexual practices as these vary across different cultures, ages, and stages of the life course.

To date, most microbicide-related behavioral research—specifically “acceptability” research—has focused on identifying optimal product characteristics for a broad range of potential users. But it is equally important to develop methods for assessing the probability that a microbicide product actually will be used consistently and correctly—not just be deemed theoretically “acceptable”—in a defined population. Emphasis should be placed on developing valid and reliable behavioral measures that will effectively predict and assess the actual use of microbicides in the context of specific sexual behaviors, and on understanding what attributes will enhance the likelihood of users selecting the product from the options available. This knowledge should inform recruitment into clinical trials, design of trial protocols, and postmarketing evaluations.

Thus, research is needed on social and behavioral factors related to product use both in the context of clinical trials and among different populations once these products are shown to be effective. Such research should be conducted in parallel with the development of different formulations of microbicide products.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Elucidate basic mechanisms of HIV transmission (virus and host factors) at mucosal surfaces that are important for microbicide research and development in diverse populations.

STRATEGIES:

Basic Biological and Physiological Research Related to Microbicides

- Identify and characterize new and understudied viral and host targets important for transmission and early dissemination in the female and male genital tracts and the rectal (lower gastrointestinal [GI] tract) and oral (upper GI tract) mucosal sites that are relevant for microbicide discovery and development.
- Determine the impact of microbicides on innate and adaptive mucosal defense mechanisms in the female and male genital tracts and the oral and rectal mucosal sites.
- Study the impact of microbicides on microbial ecology and their effects on mucosal/epithelial secretions and surfaces.
- Study intercourse physiology and discern how it relates to transmission or acquisition of HIV and the safety and activity of microbicides.
- Determine the cells or tissue types that serve as portals of entry and support subsequent spread of HIV/simian immunodeficiency virus (SIV).
- Determine the role of viral phenotype/genotype/clade and delineate the relative efficiency of transmission of cell-free and cell-associated virus in secretions at the female and male genital tracts and rectal and oral mucosal sites.
- Determine the mechanisms by which genital tract, oral and rectal inflammation, and/or infections (including STIs) may influence HIV transmission and early propagation.
- Investigate the effect of endogenous hormonal states (puberty, pregnancy, menopause, lactation-induced hypoestrogenic states, and menstrual cycles) and exogenous hormonal states (including oral contraceptive pill, hormonal replacement therapy) on the susceptibility of the female and male genital tracts to infection with HIV.

OBJECTIVE - B:

Support the discovery, development, and preclinical evaluation of topical microbicides alone and/or in combination.

STRATEGIES:

Microbicide Development and Preclinical Studies

- Develop, validate, and standardize specific, sensitive, and reproducible methods for quantifying HIV/SIV/chimeric simian/human immunodeficiency virus (SHIV) in mucosal tissues and secretions before and after use of microbicides.
- Develop, validate, and standardize specific, sensitive, and reproducible methods for quantifying immune parameters in mucosal tissues and secretions before and after use of microbicides.
- Develop, validate, and standardize specific, sensitive, and reproducible methods for assaying antimicrobial activities *in vitro*.
- Develop and support animal models to evaluate safety and potential efficacy (including the function of frequency of use) of various topical microbicides for prevention of mucosal HIV/SIV/SHIV transmission.
- Determine the extent to which *ex vivo* tissue culture models and animal models are predictive of clinical efficacy.
- Integrate genomics and informatics paradigms, concepts, and methodologies (including microchip-based technology) into microbicide discovery and development research.
- Conduct preclinical studies of potential microbicides to assess immunologic and inflammatory effects, pharmacokinetics, pharmacodynamics, toxicity in the mucosal surfaces and secretions (female and male), teratogenicity, transplacental carcinogenicity, and effects on fertility.
- Develop *ex vivo* explant models of human or nonhuman primate tissue that might provide a useful approach to (1) investigate the very early events in HIV or SIV/SHIV transmission and (2) evaluate the activity and toxicity of topical microbicides.
- Improve animal models to more closely reflect the dynamics of sexual transmission in humans. Develop animal models of HIV infection that will also be able to examine the role of co-infection with STI pathogens in HIV transmission.

- Foster the development of combination approaches, such as chemical and physical barriers, and of microbicides containing multiple active compounds with different specificities and mechanisms of action.
- Investigate the effect of endogenous hormonal states (puberty, pregnancy, menopause, and menstrual cycles) and exogenous hormonal states (including oral contraceptive pill, hormonal replacement therapy) on the safety and activity of microbicides.

OBJECTIVE - C:

Develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from the chemical, pharmaceutical, physical, bioengineering, and social sciences.

STRATEGIES:

Microbicide Formulations and Modes of Delivery

- Develop formulations, dosage, and delivery systems suitable for the genital and GI tracts.
- Develop chemical formulations lacking antimicrobial activity to serve as placebos.
- Identify and validate methods that improve the understanding of bioadhesion, biodispersion, retention, and distribution of microbicide formulations prior, during, and after intercourse.
- Study levels of systemic absorption from topical microbicide use.
- Develop and incorporate mechanisms to assess product and delivery mode acceptability in diverse populations of men and women, both within all phases of clinical studies and outside the trials setting (e.g., through focus groups).
- Understand the biologic mechanisms and physiologic changes that contribute to efficacy and safety resulting from the use of microbicide formulations, including, but not limited to, hormonal status, menstrual cycle, nature of intercourse, pregnancy, frequency of use, and sexual arousal.
- Develop methodology to analyze physical and chemical characteristics of compounds and formulations of microbicides and combinations of microbicides, including those derived from natural products.
- Develop methodology and supportive studies to characterize product traits, such as taste, smell, color, and tactile sense, that may affect acceptability and use of microbicides in diverse populations and in different types of sexual acts.
- Develop delivery systems that reduce or eliminate trauma to mucosal tissue.

OBJECTIVE - D:

Conduct clinical studies of candidate microbicides to assess safety, acceptance, and effectiveness in reducing sexual transmission of HIV in diverse populations in domestic and international settings.

STRATEGIES:

Clinical Trials of Microbicide Products

- Develop well-defined criteria for selecting the most promising products for microbicide clinical trials and for moving from Phase I through Phase III trials.
- Develop and evaluate improved methods to recruit and retain participants for Phase I, II, and III microbicide studies in the United States and abroad.
- Reassess the fundamental epidemiological principles informing clinical trials protocols including an evaluation of control group selection, statistical power, and appropriate followup time.
- Conduct research on mechanisms to improve clinical trial adherence and compliance with use requirements of products under study.
- Address ethical issues in the design and conduct of microbicide trials, including the use of placebos and control arms.
- Conduct research on ways to ensure adequate informed consent among participants in microbicide trials.
- Conduct research on the effectiveness of microbicides relative to, and in combination with, other behavioral, barrier, and therapeutic methods.
- Conduct research on the efficacy of expanding prevention choices and of hierarchical HIV prevention messages.
- Design, develop, and evaluate tools to measure product use and acceptability.
- Develop improved techniques to evaluate safety of microbicides when applied to genital and rectal mucosal and epithelial surfaces during clinical trials.

- Enhance understanding of the significance of clinical findings identified by current methods to evaluate safety, including evaluation of cervicovaginal, penile, and rectal irritation.
- Study microbicide products in HIV-infected people under treatment to determine their impact on the development of drug resistance, drug-to-drug interactions, and the potential for other adverse events.
- Develop behavioral and biological markers to evaluate safety, effectiveness, and adherence to microbicides.
- Develop methods to more rapidly ascertain HIV incidence rates among participants in microbicide trials.
- Support research on the development and dissemination of design alternatives to the randomized clinical trial (RCT) to evaluate safety and effectiveness of microbicides in individuals, groups, and communities.
- Design, implement, and evaluate Phase IV postmarketing surveillance studies once an effective and safe microbicide has been identified in Phase III trials.
- Facilitate every aspect of product development in preparation for clinical trials.

OBJECTIVE - E:

Conduct basic and applied behavioral and social science research to enhance microbicide development, testing, acceptability, and use domestically and internationally.

STRATEGIES:

Social Science Research Related to Microbicides

- Support theory-building and the development of social-behavioral models of risk and protection in the context of microbicide research.
- Conduct research on how microbicide use affects and is affected by a range of psychological, social, and cultural factors such as the following:
 - ▶ differences in expression and experiences of human sexuality (including sexual pleasure, sexual orientation, and/or sexual abuse or coercion),
 - ▶ substance use and abuse,
 - ▶ human developmental processes,
 - ▶ dynamics of intimate relationships,
 - ▶ cultural norms about gender, sexuality, fertility, and reproduction,
 - ▶ socioeconomic status, and
 - ▶ race and ethnicity.
- Study the social, structural (including economic), cultural, and demographic factors that affect access to and delivery of microbicides, as well as the implementation of microbicide intervention strategies in diverse populations.
- Develop and evaluate the efficacy, effectiveness, and cost-effectiveness of demographically and culturally appropriate behavioral and social interventions related to microbicide use in different domestic and international settings and populations.
- Support domestic and international research to improve the transfer of effective microbicide interventions to and from communities, including studies of diffusion processes and the exchange of knowledge between service providers and researchers, postmarketing research on the maintenance of effective interventions, and the generalizability of interventions among diverse populations.

- Develop improved methodologies for microbicide research, including methods for obtaining and validating self-report data, culturally appropriate standardization of measurement tools for surveys, and the measurement of change over time, based on an assessment of the current status of qualitative and quantitative methodologies for studying behavioral and social factors associated with HIV and AIDS.
- Support research to determine under what circumstances each of the following outcome measures—alone or in combination—is appropriate to use in microbicide intervention studies: behavioral measures, HIV infection, and other disease outcomes such as other STIs and blood-borne diseases.
- Develop and refine mathematical models for linking microbicide interventions with a reduction in HIV and STI incidence in different settings (i.e., as defined by levels of HIV, STIs, sexual networks, condom use).
- Develop improved and innovative methods and techniques for conducting and analyzing longitudinal microbicide studies, including improved followup methodologies, methods to increase study retention, and methods for dealing with subject attrition, missing data, and non-normal distributions.
- Foster the development, testing, and dissemination of design alternatives to the randomized controlled trial that permit ethical and cost-effective evaluation of microbicide interventions at the individual, group, and community levels.
- Evaluate the impact of culturally appropriate and age-appropriate health and sexuality education in facilitating the adoption of microbicides.
- Develop provider-focused interventions to facilitate the adoption of microbicides.

OBJECTIVE - F:

Establish and maintain the appropriate infrastructure (including training) needed to conduct microbicide research domestically and internationally.

STRATEGIES:

Infrastructure

- Establish a standing, multidisciplinary, multisectoral coordinating group with international representation whose tasks are:
 - ▶ to identify ongoing research,
 - ▶ to identify research gaps,
 - ▶ to develop strategies to accelerate development of promising products,
 - ▶ to note existing promising compounds and products, and
 - ▶ to encourage additional research to move products into use on an urgent basis (including setting realistic and monitored timeline goals).
- Establish clinical trial sites/infrastructure for Phase I, II, and III studies domestically and internationally.
- Encourage the further development of partnerships among international and national groups currently engaged in microbicide development, research, implementation, and infrastructure strengthening.
- Work with national and international regulatory bodies to address regulatory issues and structures in order to encourage more rapid development and use of microbicides.
- Identify gaps in biomedical, behavioral, ethical, clinical, and administrative training in national and international microbicide research sites, and design strategies that respond to these needs.
- Foster microbicide research training activities to encourage rapid development of national and international competitive, independent investigators (including development of mentor relationships and grant-writing skills).

- Develop strategies to strengthen training and infrastructure that will ensure that national and international microbicide research is undertaken at high ethical standards.
- Encourage development of national and international institutional capacity for microbicide research, including the enhancement of laboratory capability, data management/analysis, population-based research, high standards of conduct for clinical research, and physical infrastructure.
- Establish mechanisms to ensure that microbicide research is coordinated with, and informed by, other areas of HIV prevention research, including the development and evaluation of physical barrier methods.
- Address obstacles to microbicide research, including administrative and other barriers to international research.
- Encourage collaboration with national and international corporate enterprises, governmental and nongovernmental organizations, foundations, training institutions, and multilateral organizations involved in or concerned with microbicide research and training.
- Develop training and institutional strengthening strategies to involve national and international communities in the planning and undertaking of international microbicide research. This includes building and maintaining sites for population-based research and ensuring that communities involved in research will be prepared to benefit from the research results.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

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

APPENDIX B:

FY 2005 OAR

Planning Group for
Microbicides

FY 2005 MICROBICIDES PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ACSR	AIDS and Cancer Specimen Resource, NCI
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ART	antiretroviral therapy
ARV	antiretroviral
ATI	analytic treatment interruption
ATIS	AIDS Treatment Information Service
AVEG	AIDS Vaccine Evaluation Group
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CIPRA	Comprehensive International Programs for Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DHHS	Department of Health and Human Services
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GBV-C	GB virus (hepatitis G)
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria

GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
GRIP	Global Health Research Initiative Program, FIC
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAb	monoclonal antibody
MAC	<i>Mycobacterium avium</i> complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization

NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NK	natural killer (cell)
NMAC	National Minority AIDS Council
NNTC	National NeuroAIDS Tissue Consortium, NIMH/NIDA/NINDS
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PACTG	Pediatric AIDS Clinical Trials Group
PCP	<i>Pneumocystis carinii</i> pneumonia
PML	progressive multifocal leukoencephalopathy
RCT	randomized clinical trial, randomized controlled trial
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WRAIR	Walter Reed Army Institute of Research

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