NIAID Topical Microbicide

Strategic Plan

September 2003

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases

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Part A:

Discovery, Development, and Evaluation

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Introduction

The HIV pandemic – more than 40 million people infected, 19.2 million of them women, predominantly through sexual intercourse – has focused attention on sexually transmitted infections (STIs), both because HIV infection is a fatal STI and because other STIs are risk factors for sexual transmission of HIV. Without effective measures to prevent sexual transmission of HIV and other STIs, HIV incidence will continue to rise. In addition, STIs other than HIV cause significant morbidity and mortality, accounting for more than 17 billion dollars in costs annually in the United States alone.

A consensus has emerged that safe, effective, accessible topical microbicides are needed to prevent sexually transmitted HIV infection as well as other STIs. Such products – foams, gels, creams, suppositories, etc. – would be designed for intravaginal or intrarectal use where they would inactivate or block sexually transmitted pathogens such as HIV and other STIs. In addition to the greatest achievable efficacy against HIV and other STIs, an ideal microbicide also would be

- Completely safe for daily use
- Fast acting and long lasting
- Acceptable and appealing to both sexual partners
- Inexpensive and available without prescription
- Suitable for both vaginal and rectal application
- Available in both contraceptive and non-contraceptive formulations

Goals

The long-term goal of the National Institute of Allergy and Infectious Diseases (NIAID) is to identify safe and effective microbicides to prevent HIV/AIDS and other STIs. NIAID's near-term goal is to establish proof-of-concept (i.e., safety and effectiveness) of at least one candidate microbicide against HIV/AIDS. Once this proof-of-concept has been established, NIAID's focus will shift to product optimization in relation to the broad criteria listed previously for an ideal product.

To achieve this goal, NIAID's strategy is to support an integrated extramural program consisting of three complementary components: basic biomedical research, preclinical product development, and clinical evaluation, including behavioral research. In general, investigator-initiated grants provide funding for basic *research* that requires scientific creativity and innovation. Contracts support *development* through efficient, responsive, often high-throughput standardized product evaluation and pilot lot manufacturing processes. Cooperative agreements support clinical research, providing a mechanism for integrating extramural investigator leadership in study design and conduct with facilitation by Federal program officers and medical officers. Program

The long-term goal of the National Institute of Allergy and Infectious Diseases (NIAID) is to identify safe and effective microbicides to prevent HIV/AIDS and other STIs.

staff can provide scientific input, while also facilitating coordination among multiple programs, and with regulatory officials.

Basic Biomedical Research

NIAID believes that, in general, support of a strong basic biomedical research program will provide an innovative and improved basis for microbicide design and evaluation, help expand and diversify the microbicide pipeline, identify safe and acceptable formulations, and foster improved methods for the preclinical and clinical evaluation of microbicide candidates. Current priorities are to

- Define the molecular basis and chronology of the early steps in the infectious processes of HIV and other STI pathogens to identify multiple points at which the process of infection may be interrupted
- Characterize cervicovaginal and rectal microbial ecology and the natural defense mechanisms of cervicovaginal and rectal tissues
- Establish new and improved in vitro, ex vivo, and in vivo models to evaluate microbicide safety and efficacy
- Determine the optimal characteristics and mode of delivery of topical formulations

Preclinical Product Development of Topical Microbicides

In general, the private sector is best equipped to carry out product development. Because the private sector has been reluctant to fully engage in microbicide development, however, public sector support is needed to facilitate critical work that is currently unsupported or partially supported. A broadly active agent or combination of agents against multiple STIs will likely garner the largest market size, and therefore be the most commercially attractive product(s). Public sector and other donor support are also needed to underwrite early development and to obtain proof-of-concept against HIV, while at the same time evaluating potential use against other STIs. NIAID supports developmental activities to advance the most promising concepts to a stage where they are suitable for human testing. NIAID will

- Facilitate identification of the safest and potentially most efficacious candidate topical microbicides through laboratory and animal testing against HIV and other STIs, including
  - In vitro testing
  - Animal vaginal irritation and other animal safety studies
  - Animal efficacy
- Manufacture and, if necessary, formulate in amounts suitable for early phase clinical testing, selected, promising microbicide candidates that have proven safe in preclinical studies and that have activity against HIV, with preference given to those that have the broadest activity profile
- Work with sponsors and regulatory authorities to encourage and expedite testing of the most promising products, alone and/or in combination

Clinical Evaluation of Topical Microbicides Integrated with Behavioral Research

This stage of microbicide development is extremely challenging and complicated. Clinical evaluation must be conducted vigorously to

evaluate efficacy against all relevant STIs including HIV as well as examine short-term and long-term safety for the user and the user's partner(s). Although industry has mechanisms for conducting clinical trials, only the public sector and donors appear poised to underwrite microbicide clinical research costs. NIAID will

- Develop the clinical capacity and capability to conduct clinical trials to establish safety and efficacy/effectiveness against HIV infection in humans
- Support Phase I, II, and III clinical trials of selected, highly promising candidate topical HIV microbicides
- Help characterize critical factors associated with microbicide acceptability
- Identify strategies for improving the conduct of effective and ethical clinical trials

Future Plans

A 5-year implementation plan is proposed to support the nearer-term goal of establishing proof-of-concept for at least one microbicide candidate while simultaneously supporting basic and applied programs, which are expected to lead to a more robust and diverse pipeline of microbicide candidates for future testing as well as improved and enhanced technologies to expedite development (e.g., new and promising preclinical models for evaluating both HIV and STI safety and efficacy, new STI diagnostics).

Once the nearer-term goal of identifying and establishing the safety and effectiveness of at least one candidate product has been demonstrated clinically, NIAID will expand its focus, especially through partnerships with other agencies involved in microbicide development and dissemination, to

- Evaluate the most meaningful correlates of efficacy or effectiveness in laboratory and/or preclinical models
- Optimize protective efficacy and product acceptability, including approaches to broaden the spectrum of covered STIs
- Support and encourage technology transfer to expedite adoption of vaginal and rectal products that have proven safe and effective
- Support long-term follow-up of volunteers to evaluate long-term effectiveness and safety
- Link with others to foster relevant social and behavioral research, whenever appropriate

Introduction

At the end of 2002, the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that 42 million people worldwide had been infected with the human immunodeficiency virus (HIV), the cause of AIDS, including 19.2 million women (46 percent) and 3.2 million children under the age of 15, most of whom were infected perinatally. Of 5 million new infections in 2001, 2 million (40 percent) occurred among women. The vast majority of these infections were acquired through unprotected sexual intercourse. Unless effective prevention measures to stop sexual transmission of HIV are implemented, the number of AIDS cases will continue to grow.

The HIV pandemic has focused attention on sexually transmitted infections (STIs), both because HIV infection is a fatal STI and because other STIs are risk factors for sexual transmission of HIV. Separate from the HIV epidemic, STIs cause significant morbidity and mortality and contribute greatly to increasing health care costs. In the United States, where more than 65 million people are infected with an incurable STI, an estimated 15 million new cases occur each year, with teenagers accounting for approximately 25 percent of these new infections.[1] Excluding HIV, these infections cost in excess of $17 billion in 1994 in lost wages and health care expenditures.[2] Furthermore, in several major U.S. cities, unsafe sexual practices are on the rise, as indicated by both behavioral surveillance and increases in rectal gonorrhea and syphilis cases.

Topical microbicides, defined as preparations for intravaginal or intrarectal application that can prevent infection by HIV and other STI pathogens, represent a highly promising strategy for preventing the sexual transmission of HIV and other STIs. Topical microbicides could, in principle, inactivate virus and bacteria directly, or avert infection of susceptible cells, or block dissemination from initial target cells. The development of a microbicide for HIV (or any other STI) that meets requirements for U.S. Food and Drug Administration (FDA) licensure is a daunting task. Not only must it be effective against HIV, but also the spectrum of effectiveness against other STIs must be known, including the potential to increase susceptibility to one or more sexually transmitted agents. In addition, the short-term and longer-term safety must be well documented with sufficient follow up in Phase III studies. Furthermore, combination products, using multiple strategies to block infection, may represent the most promising approach but may require that each individual active component as well as the combination be proven safe. These factors impose substantial requirements upon the design and cost of clinical trials.

The compelling near-term need is to establish the plausibility of at least one candidate agent. Identifying a safe and even partially efficacious product would then shift the emphasis from proof-of-concept to product optimization. The following considerations guide NIAID's perspective on efficacy and effectiveness trials.

The compelling near-term need is to establish the plausibility of at least one candidate agent.

Table 1. Attributes of an Ideal Microbicide

A Topical Microbicide	
Should:	**Should not:**
• Be safe for use from one to six or more times daily over long periods of time	• Cause epithelial disruption • Induce inflammation • Be absorbed systemically
• Act rapidly and be long-lasting in effect	• Be unstable or unwieldy to store and transport
• Be acceptable to both sexual partners or completely unobtrusive	• Be messy or leaky • Cause burning or itching
• Be available in both contraceptive and non-contraceptive formulations	• Be costly or require a prescription
• Be suitable for both vaginal and rectal application	• Require use of an uncomfortable, cumbersome, or otherwise unacceptable applicator
• Act potently against HIV and/or other STIs in both ejaculate and cervico-vaginal secretions to provide bi-directional protection for both partners	• Upset the vaginal (or rectal) microbial ecology (e.g., kill *Lactobacilli* or enhance overgrowth by other pathogens)

- Safety, both short term and longer term for the user and the user's partner(s), is paramount.
- A partially efficacious product could provide insights into factors associated with effective blocking of sexual transmission: so-called correlates of effectiveness. In turn, knowledge of one or more correlates of effectiveness could accelerate identification and development of improved agents and formulations. Iterative processes like this offer the best chance to develop an optimal product.
- Demonstration of the safety and efficacy of a topical product in preventing HIV infection or any other STI (i.e., proof-of-concept) would likely remove an important barrier to increased industry investment in product development, particularly if concurrent efforts have been made to assure the existence of markets for effective products and to address concerns about corporate liability during and after the conduct of trials.

If the first product shown to be effective confers only partial protection or fails to meet all of the criteria that would be desirable in an optimal product (Table 1), new insights into correlates of effectiveness, together with findings regarding product acceptability from field experience during large-scale efficacy and effectiveness trials, can inform the development of additional products and formulations and thereby support optimization for increased efficacy, utility, and acceptability.

This strategic plan elaborates the approach of NIAID to microbicide discovery, development, and evaluation as it supports the near-term goal of proof-of-concept of at least one candidate

agent, to be followed by directed effort toward product optimization. As such, this plan

- Describes the current capacity to conduct a comprehensive program of basic, preclinical, and clinical microbicide development
- Identifies opportunities to increase capacity in specific high priority areas, especially those which NIAID is especially well positioned to address in comparison with other organizations
- Sets out plans for addressing those needs through expansion of existing resources and development of new programs
- Outlines general and specific decision criteria to be used at critical junctures to select products for prioritized development using NIAID-supported resources

Part B of this plan addresses some of the important scientific challenges associated with basic, preclinical, and clinical phases of microbicide development, and approaches that may be used to address those scientific challenges. Specifically, Part B

- Describes the current status of microbicide development including
  - Limitations of existing strategies to prevent sexual transmission
  - Progress thus far in microbicide development
  - Reasons for expecting microbicides to be an effective prevention strategy
- Elaborates remaining challenges in microbicide research and development
- Defines research efforts to address these challenges

The Organizational Framework for Microbicide Research and Development

With no substantial involvement of any major industry sponsor, microbicide discovery and development has remained the mission of domestic and international public sector organizations and foundations. Moreover, public support has only recently begun to gain momentum. Total Federal support for microbicide research in fiscal year (FY) 2001 was approximately $61,300,000, as shown in Figure 1. (The fiscal year runs from October 1 through September 30.)

The major funding agency for microbicide research and development is the National Institutes of Health (NIH), part of the U.S. Department of Health and Human Services, with approximately $47 million devoted to topical microbicides in FY 2001. This figure is expected to increase to almost $56 million in FY 2002. The U.S. Agency for International Development (USAID) was tasked by Congress in FY 2001 to establish a microbicide research and development program and allocated a budget of $12.0 million. The U.S. Centers for Disease Control and Prevention (CDC) has developed a topical microbicide program with particular emphasis on Phase I studies and development of international infrastructure for clinical testing of microbicides. A total of approximately $2,200,000 FY 2001 funds were committed to this effort.

The major funding agency for microbicide research and development is the National Institutes of Health (NIH).

Figure 1. FY 2001 Microbicide Spending – Federal

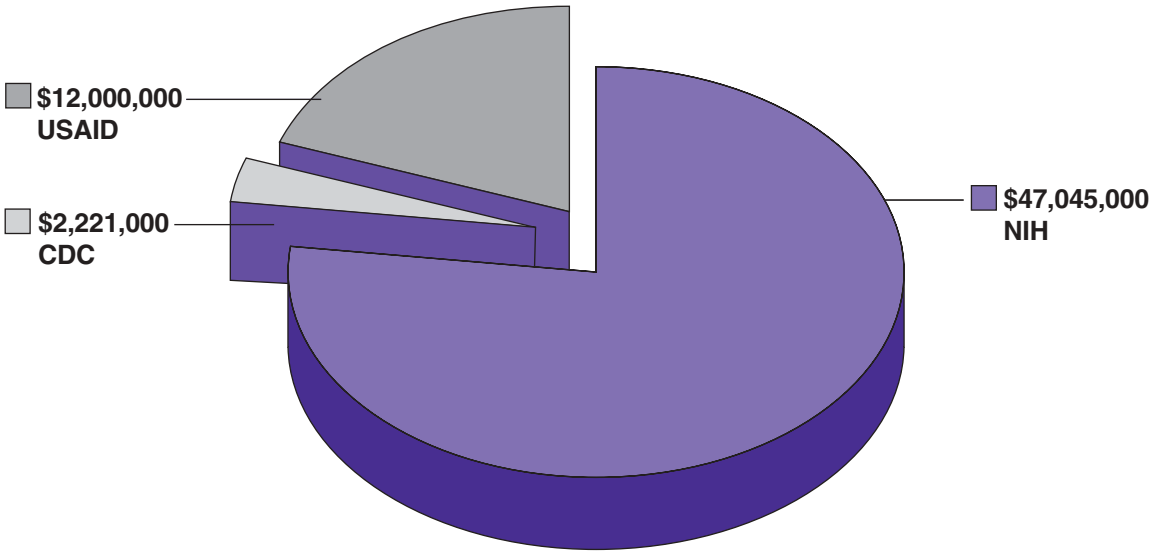
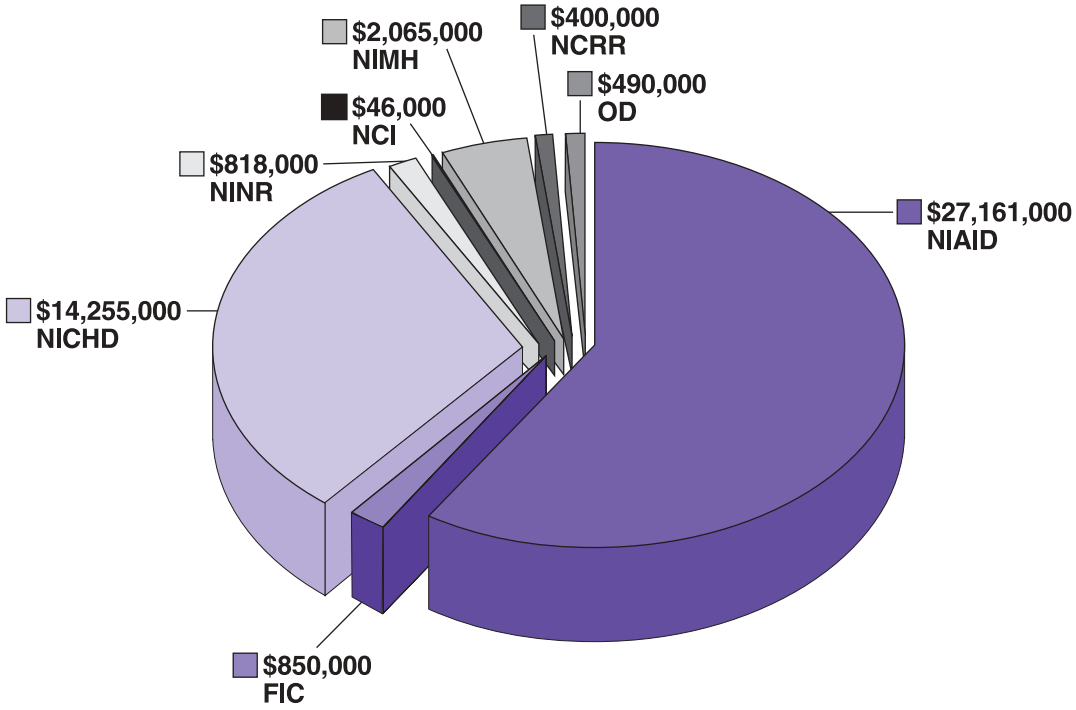


Figure 2. FY 2001 Microbicide Spending – NIH



To coordinate the NIH microbicide effort, the NIH Office of AIDS Research (OAR) convenes the NIH Topical Microbicide Working Group representing all NIH Institutes and Centers (ICs) involved in topical microbicide-related research. ICs represented on the working group include NIAID, National Institute of Child Health and Human Development (NICHD), National Cancer Institute (NCI), National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), Fogarty International Center (FIC), Office of Research on Women's Health (ORWH), and Office of Behavior and Social Science Research (OBSSR).

In response to a congressional mandate, OAR, in collaboration with other NIH institutes, CDC, USAID, and outside domestic and international experts, has developed a strategic plan for microbicide research. The microbicide component of the *NIH Plan for HIV-Related Research* (NIH Microbicide Plan), coordinated by OAR, identifies and establishes objectives and priorities and formulates policy statements to guide the conduct of NIH AIDS research related to microbicides. This plan has been formally integrated into the *NIH Plan for HIV-Related Research* for FY 2003 as a Special Area of Interest.

NIAID supports the most extensive microbicide effort at NIH, with a FY 2001 budget for topical microbicides of $27 million that increased from $19 million in FY 2000 (Figure 2). Other contributors, predominantly non-governmental, include the following organizations

- The **International Partnership for Microbicides** (IPM) – supported by a founding award from the **Rockefeller Foundation** – has secured donations from five European governments, the **Bill and Melinda Gates Foundation**, and the **World Bank** – to support its mission of mobilizing the public and private sectors of the international community to develop and deliver microbicides as rapidly as possible. IPM's missions focus on accelerating research into innovative formulation and targeted drug delivery, preclinical developmental support for high priority candidates, expansion of worldwide capacity to conduct efficacy trials, and access-related initiatives in regulatory harmonization, pricing policy, and public and policymaker awareness to improve product availability once determined to be effective against HIV transmission. Financial commitments currently exceed $70 million over a 5-year period.

- **The Contraceptive Research and Development Program** (CONRAD), partially funded by USAID and NICHD, has exploited its expertise in developing vaginal methods that prevent pregnancy to expand its mission to include the development of topical microbicides.

  - A project of CONRAD, the **Consortium for Industrial Collaboration in Contraceptive Research** (CICCR), awards grants to collaborative groups consisting of industry and nonprofit investigators, for research and development of vaginal methods that prevent STIs.

  - More recently, the **Global Microbicide Project** (GMP) has been established by CONRAD, through a $25 million grant awarded in 2000 from the **Bill and Melinda Gates Foundation**, to support development of microbicides lacking contraceptive activity over

a period of 5 years. GMP will fund both for-profit and nonprofit partnerships with an emphasis in the international arena and a focus on production of candidate microbicides according to Good Manufacturing Practice guidelines.

- The **American Foundation for AIDS Research** (amfAR) initiated a targeted microbicide program in December 1999 with the award of ten 1-year grants totaling $875,000. Following re-release of the request for proposals in February 2001, five 1-year awards were made totaling $445,000. The Foundation has committed to awarding a total of 100 1-year grants of between $75,000 and $90,000 over a period of 5 years.
- The **Alliance for Microbicide Development** is a consortium representing pharmaceutical companies, investigators from nonprofit institutions and advocacy groups dedicated to the development of topical microbicides. Funded by the **William and Flora Hewlett Foundation**, the **Moriah Fund**, **IPM**, and private contributors, the Alliance seeks to advance microbicide research and development through coordination, education, and advocacy.

As these and other programs expand microbicide research and development, careful coordination will be necessary to maximize the unique contributions each program can make to the goal of developing and commercializing microbicides that can reverse the advancing global burden of morbidity and mortality from HIV and other STIs. A formal process for coordination of governmental agencies' microbicide programs is being developed through the OAR.

NIAID Strategy for Microbicide Development

The long-term goal of NIAID is to support the development of safe and effective microbicides against HIV/AIDS and other STIs. NIAID's nearer-term goal is establishing proof-of-concept (i.e., safety and effectiveness) of at least one candidate microbicide against HIV/AIDS. Once this proof-of-concept has been established, NIAID's primary focus will shift to product optimization in relation to the broad criteria listed in Table 1 for an ideal product.

To achieve the primary and near-term goal of identifying and establishing the safety and effectiveness of at least one candidate product and to support post proof-of-concept objectives, NIAID will

- Support a strong basic biomedical research program to identify opportunities to block cervicovaginal and anorectal infection or dissemination of HIV and other STIs, thereby better understanding previously identified targets and potentially identifying new targets against which a microbicide may be developed
- Refine/develop and utilize in vitro, ex vivo, and in vivo preclinical screening and evaluation models/tools to improve and/or expand preclinical data on the likely safety and potential efficacy of various candidates or combinations
- Provide targeted support for preclinical evaluation, formulation, and production to assure that absence or limitations of industry sponsorship are not barriers to advancing the most promising candidates or combinations
- Identify and provide targeted support for the most promising candidates representing

varied modes of action, based on the assumption that robust selection of candidates will provide numerous opportunities for achieving and optimizing a protective effect

- Work with sponsors and regulatory authorities to expedite testing of promising products, alone or in combination, that block HIV at multiple stages in the infection process and prevent infection with other STIs that may potentiate HIV transmission
- Develop clinical capacity and capabilities to establish proof-of-concept in humans by evaluating promising candidates in human trials to determine safety, efficacy/effectiveness, and acceptability of candidate vaginal and rectal topical microbicides in diverse populations in domestic and international settings, particularly in populations where HIV is spreading most rapidly
- Facilitate social and behavioral research to support effective and ethical conduct of clinical trials

Once proof-of-concept has been demonstrated clinically

- Evaluate the most meaningful correlates of safety and effectiveness in preclinical models of safety and efficacy, in turn facilitating more efficient product optimization
- Optimize protective efficacy and product acceptability through continued development and formulation of more effective second and third generation products, including combination microbicides
- Conduct social and behavioral research to facilitate adoption of vaginal and rectal products that have proven safe and effective

The comprehensive NIAID microbicide strategic plan is configured to address, through programs and workshops, the scientific challenges that span basic, preclinical, clinical, and behavioral research.

Comprehensive Microbicide Program

The comprehensive NIAID microbicide strategic plan is configured to address, through programs and workshops, the scientific challenges that span basic, preclinical, clinical, and behavioral research (see Part B), while providing targeted support to advance the development of priority products without adequate corporate support. This section describes established programs and opportunities for their expansion, as well as new programs that could accelerate the field. The latter includes a novel public-private program that uses milestone-driven funding to expeditiously advance promising microbicide concepts through preclinical testing and into early clinical development. This section also defines current capacities and analyzes opportunities for increased capacity in critical areas.

Organization of the NIAID Topical Microbicide Program

The NIAID topical microbicide program seeks to advance microbicide research and development across the microbicide development pathway. Accordingly, the program does not manage a specific portfolio of candidate microbicides or seek to function solely as a "virtual pharmaceutical company." Rather, the overall strategy depends on a broad overview of the field that assumes the full spectrum of research – from basic through clinical – requires support, but that NIAID resources should be focused on particular areas where a unique contribution can be made. In some cases, that contribution will be through support of basic scientific research through grants that underwrite fundamental studies that lack other sources of support such as pharmaceutical research and development investment or other public sponsors. In other cases, NIAID provides developmental resources for targeted purposes to advance a specific, promising candidate through a particular phase of preclinical evaluation, such as in vitro or animal model testing where sponsor expertise or capacity is limited.

Management Across Divisions and Programs

Because the NIAID topical microbicide program ranges across basic, preclinical, and clinical components of microbicide research and development, it draws on a corresponding range of staff expertise from basic and applied science as well as clinical investigation. Because it seeks to evaluate the potential activity of microbicides against both HIV and other STIs, it integrates staff from the NIAID Division of AIDS (DAIDS) and Division of Microbiology and Infectious Diseases (DMID).

To integrate staff across programs and divisions into an effectively coordinated, functional unit, the NIAID Topical Microbicide Working Group (NIAID TopMic Group), consisting of all NIAID staff with substantial involvement in microbicide research and development (see Attachment 1: NIAID TopMic Group Membership), has met no less than monthly for several years under the leadership of the Topical Microbicide Team Leader in DAIDS. TopMic Group meetings include presentations by sponsors of preclinical data to support prioritization of candidates for access to developmental resources, identification and specification of new initiatives to address potential gaps in the program, and integration of NIAID activities within the framework of the NIH Microbicide Plan and the mission of other Federal and non-Federal stakeholders in microbicide research

and development such as NICHD, CDC, and IPM.

Although alternative organizational structures have been considered in which all staff with major involvement in microbicide research and development would be segregated into a separate administrative unit, the prevailing view is that the NIAID TopMic Group provides effective coordination and program management without sacrificing important collegial and professional interactions with the parent programmatic areas in which individual staff are situated. For example, separating those TopMic staff in DMID from their DMID colleagues in a separate administrative unit might make it more difficult to integrate into the microbicide effort state-of-the-art knowledge of STI transmission, infection, pathogenesis, and diagnosis, without providing an offsetting benefit in improved coordination and management of microbicide-specific research and development activities.

Utilization of Preclinical Contract Resources

Another important principle of TopMic management relates to the utilization of contract resources, especially in the area of preclinical development. Responsible management of scarce contract resources – including mandatory Federal guidelines that require official approval to allocate funds for specific subtasks, and contracts that specify Federal officials as the recipients of contract deliverables – requires ongoing involvement of project officers in the oversight of activities supported by preclinical development contracts and in interactions between product sponsors and developmental resource contractors.

With a planned expansion of preclinical contract resources, NIAID plans to create a new standing review group of external experts to assist in prioritization. This Microbicide Developmental Resources Group will review and make recommendations to the TopMic Group on requests over $250,000.

Coordination with Other Federal Agencies and Resources

From a product development perspective, the NIAID TopMic Group has identified two areas where increased coordination might accelerate progress: technology transfer and regulatory review.

Although Federal grants and research and development contracts contain provisions that favor commercial development of innovative concepts and products, promising designs and candidate molecules may languish in the research literature and laboratories of inventors without specific incentives to move these approaches into commercial development. This may be especially true in the area of topical microbicides where there is minimal active involvement from the pharmaceutical industry to commercialize promising candidates. To expedite transfer of promising technologies into a development framework, the TopMic Group has begun to initiate meetings with NIAID staff responsible for facilitating technology transfer, especially from university and research institute settings, into commercialization frameworks, to identify incentives and other strategies to foster this transition.

In addition, a new Development Resource Master Contract (see below) includes a subtask in which contractor staff will facilitate technology transfer for specific microbicide candidates.

DMID and DAIDS have increased the number of staff with substantial experience at FDA.

The TopMic Group has begun to work with these staff to facilitate communication between product sponsors and regulatory reviewers (such as active encouragement of pre-investigational new drug [IND] teleconferences), assist in interpreting FDA guidance documents and comments, and identify broad areas where joint NIH-FDA meetings might help clarify, expedite, or facilitate regulatory guidance and review.

Basic Biomedical Research

A strong basic biomedical research program represents the foundation upon which microbicide design and evaluation is based. The identification of a promising microbicide candidate is facilitated by understanding the molecular basis and chronology of early steps in the infectious processes of HIV and other STIs in the context of cervicovaginal and rectal tissue ecology and natural defense mechanisms. NIAID supports this research predominantly through investigator-initiated grants that include studies to

- Define the HIV and STI entry processes and identify the first cell infected
- Understand the role of different cell types and host factors in facilitating transmission and spread (e.g., co-receptor and DC-SIGN expression and utilization); compartmentalization of HIV genital secretions
- Elucidate the role of STIs and local inflammatory processes and cytotoxic T lymphocytes in transmission
- Determine the impact of therapy on viral load in genital secretions and transmission
- Characterize viral diversity at the time of infection in women and the role of sex hormones and hormonal contraceptives in transmission
- Delineate the role of hereditary, innate, and acquired resistance to infection
- Characterize the antimicrobial components of vaginal fluids

Investigator-initiated grants also have been funded to establish new and improved models to evaluate microbicide safety and efficacy and to understand the optimal characteristics of topical formulations. Grants focused on model development encompass projects on in vitro models using continuous cell lines and primary cells in the presence of additional components to mimic genital secretions, ex vivo tissue-based models, and in vivo murine, feline, and nonhuman primate models, including a rectal transmission model. Grants focused on formulation science include projects to evaluate the transport and activity of microbicide formulations (e.g., alterations of tissue permeability and effect on microbicide efficacy) and distribution of microbicide/formulation in vivo.

To further stimulate new approaches for microbicides, NIAID recently launched an innovation grant program in AIDS research. This program supports early, high-risk, short-term projects that may be able to move a novel approach to the point where it can successfully compete for support via more conventional grant mechanisms (e.g., R01). Specific areas targeted under the current program that bear on microbicides include

- Viral and cellular processes involved in transmission, local propagation, and spread of HIV
- Processes for cervicovaginal and rectal transmission of HIV
- Improved methods of formulation and delivery

Table 2. NIAID Microbicide Development Capacity

Contract Resource			Microbicide Evaluations		Capacity/Year
			FY 2000	FY 2001	
In vitro Virologic Testing					
	Primary screen/HIV		543	441	450
	Secondary screen/HIV		58	56	60
	Primary screen/HSV		16	14	50
	Secondary screen/HSV		16	14	50
Chemical Synthesis			8	7	4
Safety					
Rabbit Vaginal Irritation Test					
	Unformulated		2	4	
	Formulated		2	3	12
Vaginal Absorption			1	4	9
Analytical Methods			1	2	4
Process					
Formulation Development			0	0	3
Clinical Product Manufacture			0	0	2
In vivo HSV-2 testing					
	Mouse		25	32	64
	Guinea pig		0	8	16
Nonhuman Primate Testing					
	Safety		3	7	
	Chlamydia efficacy		0	3	8
	SIV/SHIV efficacy				
		Vaginal	2	2	
		Rectal	Not available	2	4
Additional Toxicity Testing					
Chronic Toxicity			Not available		
Reproductive Toxicity					
	Segment I		Not available		
	Segment II		Not available		
	Segment III		Not available		
Carcinogenicity			Not available		

- Preclinical systems to test microbicide safety and efficacy

Preclinical Product Development and Selection

Although, in general, product development is most efficiently executed by the private sector, public sector support is needed to facilitate critical work that academic and smaller industrial sponsors lack sufficient resources and mechanisms to address. In addition, a broadly active agent or combination of agents that prevents transmission of HIV and other STIs simultaneously will be most commercially attractive in garnering the largest market share and is therefore the ultimate goal. A focus on HIV prevention will most likely yield products

that are of greater public health importance for populations with very limited resources, but of reduced commercial appeal, thus making public and donor support pivotal. NIAID preclinical development resources have been established to help address needs in several key areas.

In Vitro Screening

In Vitro Screening Against HIV

An NIAID-supported contract designed to support microbicide and therapeutic development provides microtiter-based, high-throughput assays to evaluate uncharacterized compounds for activity against HIV. The testing algorithm is initiated with separate primary screening assays that separately target CD4-independent and CD4-dependent cell-to-cell virus transmission. Compounds found to be active in either or both of the primary screens (criteria defined on page 24) proceed to the second phase of the testing algorithm. The second phase includes: (i) repetition of the primary screens in the presence of mucopoly-saccharides to mimic the vaginal environment; (ii) evaluation of the effect of the compound on several species of *Lactobacillus* that represent beneficial natural flora in the vagina; and (iii) secondary assays to measure inhibition of virus-cell attachment (CD4-gp120 interactions) and cell-cell fusion. A CD4-independent assay was recently developed to monitor the activity of potential topical microbicides in the pH transition range of 4.5 to 7.4 to mimic the vaginal conditions during coitus. This assay will soon be integrated into the testing algorithm as a secondary screen. Should a microbicide candidate meet all the in vitro criteria, it will be advanced to the next stage of evaluation in the rabbit vaginal irritation and other safety assays. These criteria may need to be re-examined as additional information becomes available as well as when new/improved models are identified. This screening contract is currently being used to capacity (Table 2), which is about 500 evaluations per year. (NOTE: Capacity is defined as the number of evaluations per year and not the number of distinct agents per year [e.g., varied formulations or doses of the same agent may be tested]).

In Vitro Screening Against Human Herpes Simplex Virus (HSV)-2

A contract for therapeutic and microbicide development provides two levels of in vitro screening against HSV-2. A primary screen measures inhibition of cytopathic effect (CPE) following pretreatment of human foreskin fibroblast (HFF) cells with an uncharacterized microbicide candidate. Candidates with activity in the primary screen are subjected to a secondary in vitro screen using the more reliable and labor-intensive plaque reduction assay in HFF cells. Those compounds with microbicide activity documented in preliminary evaluations by outside investigators are evaluated directly in the plaque reduction assay. Capacity (Table 2), which is 100 evaluations per year, currently exceeds the level of requests for testing.

NIAID preclinical development resources have been established to help address needs in several key areas.

In Vitro Screening Against Other STIs

Currently, NIAID has no resources for screening microbicide candidates against STIs other than HIV and HSV. Given the association of specific STIs with enhanced HIV transmission, information regarding the spectrum of microbicide activity of a particular candidate is desirable, especially for *Neisseria gonorrhoeae, Trichomonis vaginalis*, and *Chlamydia trachomatis*. Testing resources for these pathogens are not currently available but have been identified as a potential area for expansion in the proposed 5-year plan.

In Vivo Animal Safety Testing

A contract to conduct preclinical toxicology and pharmacokinetic evaluations for therapeutics and microbicides provides several different types of general and specialized safety testing on microbicide products. Both bulk drug substance and final clinical product are evaluated for their potential to irritate the vaginal surface using a standardized animal model, the rabbit vaginal irritation model (RVI), accepted and recommended by FDA for testing of vaginal products.[3] Results are expressed as a numerical value representing an index of both incidence and severity of irritation.

Absorption into the blood and distribution to other tissues also are routinely measured. Model development studies have been conducted to evaluate the rate and extent of distribution of test compounds throughout the vagina and associated reproductive/excretory organs. If needed, systemic toxicity studies can be conducted for agents that are absorbed systemically. Standard genetic and immunologic toxicity studies can be conducted routinely on candidate microbicides. Capacity significantly exceeds current use of this resource. Twelve RVI evaluations and nine vaginal absorption studies per year can be accommodated in this contract. Over the past several years, approximately $200,000 per year has been spent on this effort and the current contract has been expanded to permit up to 2 to 3 times that amount if needed (Table 2).

The Sexually Transmitted Disease Prevention-Primate Unit (STDP-PU) contract was awarded to assess topical microbicide candidates for toxicity to cervical/vaginal tissues after repeated application in pigtailed macaques *(Macaca nemestrina)*.[4] Although this model is not considered a critical path for microbicide development, the similarity of the *M. nemestrina* cervicovaginal anatomy, microflora, and pH to that of humans may make the pigtailed macaque a more relevant model than the RVI. The Topical Microbicide Program Projects have supported promising preliminary studies to establish a *M. nemestrina* model to evaluate toxicity profiles for rectal microbicide candidates. Expansion of contract resources would be required to make this rectal model available to microbicide sponsors. The contract is currently able to meet needs at the existing capacity, which is 8 to 10 vaginal safety or efficacy evaluations per year (Table 2).

The ability of these methodologies to predict what will happen in humans in controlled clinical trial settings and subsequently, their relevance to real-world product use where patterns of frequency and duration may vary widely is unknown. This gap in understanding presents an opportunity to learn from other areas, such as ophthalmic products and the cosmetic industry, where the safety of frequently applied products may be evaluated in the rabbit eye irritation test. Additional research on the applicability of such models for evaluating microbicide safety has been identified as a potential area for expansion in the 5-year plan.

Resources to support reproductive toxicology as well as carcinogenicity and chronic toxicity, required by FDA, are not currently available in the NIAID program, but have also been identified as a potential area for expansion in the proposed 5-year plan.

Preclinical In Vivo Efficacy Testing in Animal Models

Mouse and Guinea Pig Models of Genital HSV-2 Infection

A contract provides mouse and guinea pig models of human herpes virus disease, including genital herpes.[5] Capacity exceeds current use of this resource, which is 64 mouse and 16 guinea pig evaluations per year (Table 2).

Nonhuman Primate Model of Chlamydia

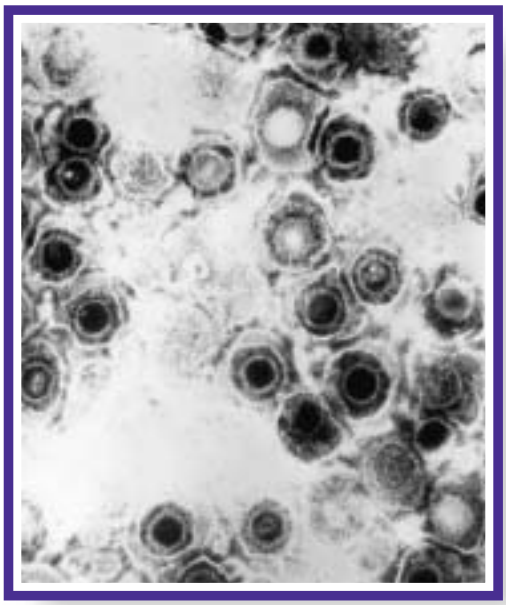
Once a microbicide candidate has been shown to be safe in the *M. nemestrina* model, the potential efficacy of the microbicide to prevent chlamydial infection of the cervix is evaluated in *M. nemestrina* through the STDP-PU.[6] The contract is currently able to meet needs at the existing capacity, which is 8 to 10 safety or efficacy evaluations per year (Table 2).

Nonhuman Primate Models of HIV

The capacity and expertise for evaluating the efficacy of candidate HIV microbicides in nonhuman primates are distributed among several contracts.[7] Because there is no information yet as to which model most closely parallels results in humans, and because each testing facility is generally focused on a single macaque species and on only one well-characterized, relevant SIV and/or SHIV strain, several models are currently being used. The models are

- Pigtailed macaques challenged with SHIV89.6P, a virus which contains a dual tropic HIV Env from a patient isolate
- Indian-origin rhesus macaques (*Macaca mulatta*) challenged with SHIV89.6P
- Indian-origin rhesus macaques challenged with SIVmac251

SHIV strains generally are more susceptible to entry inhibitors and must be used to evaluate microbicide candidates with this proposed mechanism of action. In order to detect a protective effect afforded by the candidate topical microbicide, all untreated animals in a study must be infected after exposure to virus. To enhance susceptibility to viral infection and ensure infection of 100 percent of control animals, a single dose of progesterone is typically administered one month prior to the vaginal administration of virus. Nonhuman primate models can be used to optimize dose and timing of microbicide application and to enhance understanding of microbicide mechanism of action. For example, a microbicide candidate that acts by inhibiting reverse transcription may require absorption into mucosal tissue, prompting a longer interval between application of product and exposure to HIV than a product that acts directly by inactivating virus. Contract support for evaluating the safety and efficacy of topical microbicides in the nonhuman primate model will continue to help identify microbicide candidates with the ability to block vaginal SIV and SHIV infection in macaques, and provide parallel evaluations of microbicides that have already advanced into human clinical trials. Current capacity is four evaluations per year (Table 2).



Efforts are underway to refine the nonhuman primate models to more meaningfully simulate the real-world process of infection using the following approaches

- Dual HIV/STI infection
- Multiple low-dose virus inoculations in concert with repeated applications of microbicide
- More relevant viral strains that represent the dominant phenotype in recently infected individuals
- Chinese-origin rhesus and cynomolgus macaques

To address limitations of in vitro and animal model systems, NIAID proposes to utilize distinct, but redundant, preclinical test systems for each critical step in the discovery and development pathway, so that as products complete safety and efficacy evaluations in human clinical trials, results from a range of preclinical test systems will be available for comparison with clinical results to determine which of the preclinical systems correlated most closely with the clinical results. In turn, the clinical data will be used to identify the most relevant among the existing models and to optimize and refine the models to make them more predictive. Alternatively, safety and efficacy in human populations may warrant efforts to develop new models, should the existing models prove to be of little relevance. In view of the increasing costs associated with macaque studies and the level of requests, additional capacity will be needed to ensure the continued utilization of animal models to prioritize microbicide candidates suitable for advancement using public sector support.

Production of Reagents and Products for Preclinical and Clinical Evaluation

Chemical Synthesis

A contract to provide synthesis of pure chemicals for preclinical discovery and development and for clinical trials of microbicides, tuberculosis drugs, and HIV drugs is currently funded at slightly more than $400,000 per year, with a waiting list of several months for availability. In the past 2 years, synthesis of eight compounds for early microbicide discovery studies (Table 2) has been undertaken. As microbicide discovery and screening efforts increase, additional resources will be required.

Formulation Development

A contract to provide clinically acceptable formulations or delivery vehicles – for both water-soluble and lipid-soluble microbicides – includes all of the standard preformulation studies that any drug requires before a concerted formulation development effort begins.[8]

In the past 2 years, no microbicide formulation work has been conducted (Table 2) but, should

several new candidates require such assistance and resources concurrently, additional formulation support would be needed.

Advanced formulation work – both general development of innovative formulations specifically applicable for generic types of topical microbicides in development and intensified efforts to apply innovative formulation technologies to promising candidates in the pipeline – remains a high priority. The NIAID TopMic Group will seek to establish a partnership with IPM and others working in this area to maximize the most efficient and expeditious use of available resources.

Clinical Product Manufacture

The formulation contract described above also provides capacity to manufacture products in amounts and to specifications required by law for Phase I/II clinical trials. This contract is shared by all clinical trial programs supported by DAIDS, however, with the effort focusing principally on meeting ongoing requirements for oral medications for therapeutics research. Should this resource be required for future microbicide development plans, additional contract support and resources would be required.[9]

Expanded Product Evaluation and Development Capacity

Based on recognition of needs for increased preclinical development resources and more flexible and responsive mechanisms for securing resources as needs and opportunities become clear, NIAID has initiated two new mechanisms expanding product research and development efforts: first, a master contractor and, second, a contracted program to expedite preclinical development and initial clinical evaluation of selected candidates.

Development Resource Master Contract

NIAID has received concept approval to develop an FY 2003 initiative for a preclinical development contractor in the area of both HIV vaccines and topical microbicides. Primary areas of effort would include project management, process development and production, safety testing, regulatory documentation, and information and data management.

This contractor would have the administrative capacity to rapidly evaluate, qualify, select, and enter into subcontracts with preclinical development contractors that can provide resources for all phases of preclinical development, including product development, clinical lot production, formulation, preclinical enabling studies, and associated tasks leading to the filing of IND applications.

In addition, this contract would support scientific staff who have advanced training sufficient to qualify them to interpret and summarize preclinical product data – including the details of methodologies used among different laboratories and algorithms to score outcomes – and to establish databases and generate reports that can facilitate decision-making among program staff.

Microbicide Design and Development Team Contracts

NIAID has received concept approval to adapt a strategy that has expedited HIV vaccine development, which would implement microbicide design and development team contracts. Although expediting product development can be facilitated by targeted support for specific individual requirements such as preclinical testing or GMP manufacture of pilot clinical lots, successful HIV vaccine

development efforts suggested that a parallel strategy could create a more seamless and therefore efficient approach, especially if it fosters and benefits from industry expertise in product development.

These contracts would be designed to advance promising candidates through all stages of IND-enabling studies. They would be awarded – following peer review for scientific merit and budget appropriateness – to sponsors who provide persuasive evidence of the microbicide candidate's potential efficacy and safety, and who propose a clear, focused plan for moving products through the development process.

The contracts would be structured to provide for release of additional increments of funding upon achievement of specific developmental milestones, thereby maintaining continuity in a development program while assuring program participation in the determination of satisfactory progress. This approach would have the further advantage of focusing resources on IND-enabling studies and GMP process manufacture required to qualify a candidate for clinical trials, without diverting resources to fundamental research issues that can be more appropriately supported by separate unsolicited grants or other programs.

Phase I Through Phase III Clinical Evaluation

NIAID supports the full range of clinical microbicide trials, from pilot Phase I safety evaluations through large-scale efficacy and effectiveness trials.

The pilot Phase I evaluations are supported by the Integrated Preclinical-Clinical Program on HIV Topical Microbicides (IPCP-HTM). By design, this program supports iterative research in which the findings from small pilot clinical evaluations inform further laboratory studies directed at reformulation or other modifications to optimize the microbicide candidate.

Expanded Phase I through full-scale efficacy/effectiveness trials receive support through investigator-initiated grants, including the HIV Prevention Trials Network (HPTN), which lists microbicide research as one of its highest priorities.[10]

Products thought to have efficacy against STIs other than HIV enter into trials through the Sexually Transmitted Diseases Clinical Trial Unit program supported by DMID. To date, no microbicide candidates have successfully completed the preclinical testing necessary for evaluation in this program.

Phase I trials are conducted to collect early safety data of increasing dosage and frequency of application. Typically, such studies begin with women at lowest risk of HIV and STI exposure – either sexually abstinent or in a mutually monogamous relationship with a low-risk partner. Once a maximum safe dosage and/or daily frequency of application is established, additional Phase I studies are carried out to evaluate product use by small numbers of sexually active HIV-infected women.[11]

Initial Acceptability Findings

The earliest users of new products, in Phase I studies, may provide preliminary information on major considerations related to product acceptability. In addition, Phase I trials may support focus groups among the male partners of trial participants who – although advised to use a condom to avoid exposure to the investigational agent – give some early indications as to how the partners of users in larger trials might respond to use of the product by their

female partners. Although acceptability concerns identified at this stage of product evaluation would not be expected to interrupt further product development unless the product was overwhelmingly unacceptable, they do provide information that may be used for educating, counseling, and assessing acceptability among participants in expanded trials.

Male Tolerance Studies

As clinical trials enroll women at higher risk – with multiple and/or casual partners – requiring all consenting male partners to use condoms or explaining the risk of exposure to an investigational product ceases to be feasible. In addition, products that appear to be free of vaginal toxicity would be undesirable if found to cause lesions to penile epithelium or mucosa. Accordingly, Phase I trials now include "male tolerance" studies that evaluate up to twice daily exposure of the circumcised and uncircumcised male penis to investigational microbicides. These studies are designed to assure that products that advance into Phase II trials are free of clinically significant side effects such as macroscopic lesions.

Rectal Safety Studies

Topical microbicides are currently being developed primarily for use in preventing HIV transmission during penile-vaginal intercourse. It is understood however, that eventually users may generalize findings of vaginal effectiveness to assume such products may be safe and effective if applied rectally. Accordingly, product development has begun to assess rectal toxicity of products initially designed for vaginal use, and initial clinical work is now underway under NIAID support to establish suitable safety parameters for Phase I rectal toxicity studies that would be considered part of the routine development plan for qualifying topical microbicides to advance into Phase II testing. For those products shown to be efficacious for vaginal use, evidence of rectal safety can provide additional assurance that off-label rectal application would not be harmful, and also might facilitate entry of products deemed feasible and plausible for rectal protection into trials evaluating their effectiveness for that indication.

Expediting Clinical Efficacy/ Effectiveness Trials

Conventionally, the clinical development process would next proceed to Phase II trials that enroll larger populations at higher risk of infection representative of those who would be included in large-scale efficacy or effectiveness trials, to collect expanded safety data while evaluating biological indicators of the plausibility of protective efficacy. However, no definitive biological correlates of effectiveness against HIV have been determined for topical microbicides, although rates of acquisition of other STIs may be indicative of potential anti-HIV activity in the case of broader spectrum microbicides. Consequently, to expedite the product evaluation process,[12] the separate Phase II trial has been eliminated in the current testing paradigm. Now the first subgroup (10 percent of participants) in Phase III trials will be rigorously assessed for any adverse responses to the candidate microbicide following a visit schedule, including intensive clinical assessments such as colposcopy that otherwise would be employed in a Phase II trial. Issues related to the dose and schedule –

NIAID supports the full range of clinical microbicide trials, from pilot Phase I safety evaluations through large-scale efficacy and effectiveness trials.

ordinarily established during Phase II trials – are addressed in one or more Phase I studies.

Capacity Building

The HPTN – the principal NIAID-supported mechanism for supporting Phase I through III clinical trials of microbicides – offers important advantages including

- A global network of clinical trial sites offering access to a diverse array of at-risk populations, permitting multicenter evaluations of candidate products
- A multidisciplinary and interdisciplinary scientific leadership structure to facilitate cross-fertilization of ideas among investigators with diverse areas of expertise, and an effective integration of basic, clinical, epidemiologic, social, and behavioral scientific expertise
- Procedures for continuous assessment of the integrity of trial conduct, data collection, and data management – together with provisions for on-site remedial training as needed – which complements the oversight responsibilities of an independent Vaccine and Prevention Data and Safety Monitoring board convened by DAIDS to monitor Phase III trials

As elaborated in Part B, substantially expanded capacity for global efficacy and effectiveness trials will be necessary, even with a parsimonious approach to product selection. Important considerations include a need to evaluate multiple products in diverse high risk populations so that

- Safety is rigorously assessed in relatively large and diverse populations using the product under varied conditions of background health, STI exposure, use-frequencies, etc.
- Efficacy is not underestimated, for example, as a result of acceptability problems impairing consistent use, or due to higher than expected rates of rectal exposure to HIV
- Sufficient generalizable efficacy data precede widespread deployment in populations among whom direct measures of efficacy have not been conducted, so that the potential impact of reduction in condom coverage can be assessed relative to product effectiveness
- The first product shown to be safe and efficacious will likely confer only partial protection and may not necessarily meet all other criteria (e.g., availability in both contraceptive and non-contraceptive formulations, efficacy against other STI pathogens). Iterative cycles of efficacy and effectiveness testing will guide optimization of microbicide candidates and further testing. However, with partially effective products (as well as condoms) employed as controls – rather than an inert placebo – substantially larger populations will be required to measure even relatively large additional gains in efficacy

In turn, developing an adequate clinical research infrastructure will require a substantial investment in capacity-building, especially in resource-poor countries where the need is greatest. Pivotally important needs include

- New construction or renovation together with necessary equipment
- Scientific training at all levels
- Community education and mobilization efforts
- Adequate preparatory work will insure that, especially for large trials, the investment of financial resources and the voluntary efforts of thousands of trial participants lead to reliable

and interpretable findings. Before large-scale trials begin, the responsible organizations should have established their capacity to

- Accrue study cohorts efficiently
- Retain very high proportions of study participants over long periods of follow-up
- Adhere to the highest ethical and operational standards for trial conduct, data collection, and clinical and laboratory assessment

To enhance clinical research capacity, particularly in developing countries, NIH supports a variety of targeted and general programs.

- In order to maximize the flexibility and available resources for clinical trials, NIAID has issued a request for proposals for a clinical research organization or consortium of organizations capable of implementing, managing, and monitoring global HIV prevention and therapeutic trials. This resource can – depending on need, opportunity, and available resources – be expanded to enlarge worldwide capacity to advance promising microbicide candidates prioritized by NIAID into all stages of clinical trials.
- The DAIDS Comprehensive International Program for Research on AIDS (CIPRA) provides support for HIV-related prevention and treatment research that specifically addresses the AIDS research priorities identified by in-country scientists and policy makers. Even if the specific projects do not directly address microbicide development, this program will enhance overall in-country clinical research capacity, including expertise in the design and conduct of clinical trials.
- OAR provided $2.7 million in FY 2000 to enhance research facilities and equipment at developing-country clinical sites in the HPTN.
- FIC supports a variety of programs to increase the scientific and logistical capacity of developing countries in support of clinical and epidemiological research.[13]
- DAIDS supports independent contractors to monitor the conduct of all DAIDS-sponsored clinical trials, including both those conducted within networks such as the HPTN and those conducted through investigator-initiated grants.[14]

Upon demonstration of the efficacy and effectiveness of microbicides in global clinical trials, their long-term safety – for the microbicide user, the user's partner(s), and children born to a microbicide user – must be established. Given the limited timeframe of grant and contract support available through NIAID, the Institute will explore partnerships with other agencies with demonstrated expertise and capacity in long-term surveillance (e.g., CDC) to provide for continuing follow-up of trial volunteers to evaluate long-term safety.

Social and Behavioral Research on Microbicides

Phase III trial designs have been modified to accommodate findings from previous efficacy trials in areas such as behavioral assessment, and have integrated acceptability research into the design of all phases of research, beginning with the first Phase I trials. The interdisciplinary scientific leadership structure of the HPTN facilitates these efforts.

In addition to the programs just mentioned, other NIH programs complement these efforts and those supported through investigator-initiated projects.[15]

The economics of microbicide development – the market potential for effective products, subsidy mechanisms, and means of addressing concerns about intellectual property and liability – remain inadequately addressed. This gap, ideally, might be addressed by the non-profit sector, including IPM, which may adopt strategies similar to those developed by the international AIDS Vaccine Initiative (IAVI) to call attention to the need to increase private sector investment in vaccine development and address product access.

Criteria for Advancement of Candidate Microbicides

Although expansion of specific programs will be necessary to enlarge the pipeline of promising microbicide candidates, priorities must be set at specific junctures in the development process to assure efficient use of resources. As outlined in the accompanying discussion of scientific challenges, the need to prioritize products becomes particularly acute for large-scale clinical trials where even the most vigorous efforts to expand clinical trial capacity is not likely to keep pace with a proliferation of plausible candidates. Particularly when multiple candidates are drawn from the same family of compounds and expected to act via an equivalent presumed protective mechanism, a lead candidate needs to be identified during either preclinical or early clinical development.

For advancement into Phase I trials, NIAID will actively support further development only of those colorless or lightly colored candidates that meet the following criteria during initial in vitro screening

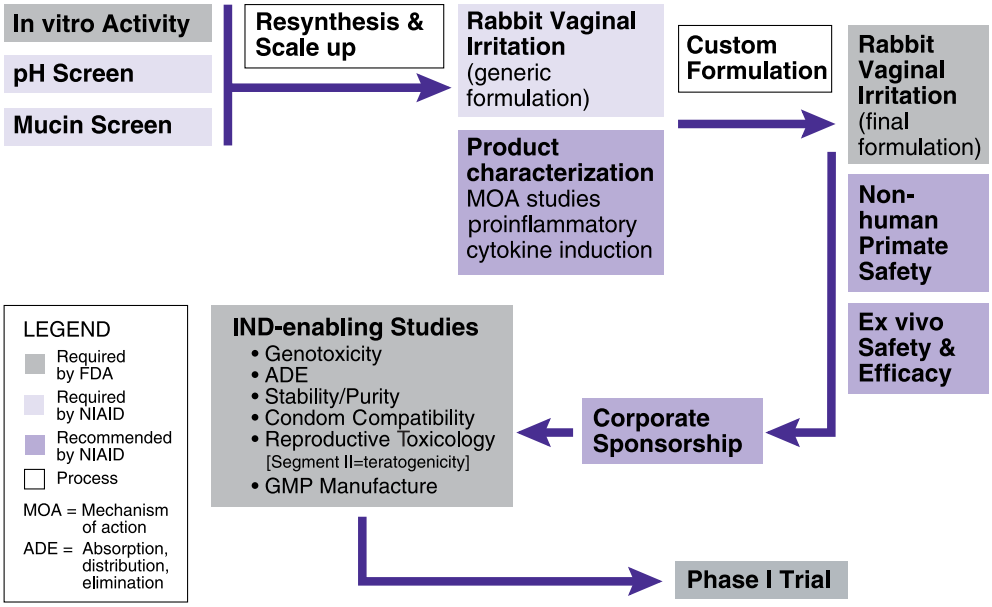
- IC_{90} less than or equal to 50 µg/ml in a primary screen; priority will be given to candidates meeting this criteria in both primary screens
- IC_{90} less than two-fold decrease when tested in secondary screens to evaluate effect of pH and mucin
- Therapeutic index greater than or equal to 50

A microbicide candidate that satisfies these criteria may be advanced to preclinical safety testing in the RVI model following formulation in a generic vehicle such as K-Y jelly. Mechanism of action studies of previously uncharacterized candidates can be conducted simultaneously.

Safety in the RVI model must be demonstrated in order to qualify for further development, using NIAID preclinical resources. With a composite score range of 0 to 16, acceptable candidates score in the 0 to 8 range, the 9 to 10 range is considered borderline and a score ranging from 11 to 16 is unacceptable. Nonoxynol-9 (N-9) generally scores between 8 to 12. Those

Priorities must be set at specific junctures in the development process to assure efficient use of resources.

Microbicide Phase I Development Path



candidates that score as poorly as the N-9 standard (1.0 ml of Conceptrol), run in parallel, will not be considered for further advancement. Candidates that score better than N-9, between 1 and 4 (as described in Eckstein et al. J. Reprod. Fertil. 20: 85 [1969]) will be given highest priority while those with a score more than 4 but less than the score for the N-9 standard will be advanced in priority order based on additional considerations, such as mechanism of action, potential cost, etc. In addition, cost and breadth of activity are factors considered throughout the development process.

A product development plan to advance a compound through preclinical development and clinical evaluation must be customized to take into account the specific physicochemical (e.g., immunogenicity or hypersensitivity potential) and biological (e.g., mechanism of action, potential toxicities) characteristics of the active agent. For example, a microbicide candidate that acts intracellularly must be absorbed in order to prevent infection. Systemic absorption and toxicities must then be closely monitored to address safety concerns.[16]

Because in vitro and ex vivo and preclinical correlates of safety among human product recipients remain incompletely characterized, the overall strategy for advancement from preclinical to clinical testing will seek to advance products into human trials as expeditiously as possible to obtain readouts of human safety.

Additional preclinical methods to evaluate safety are emerging from new ex vivo and animal models of safety and efficacy, newly developed assays to evaluate proinflammatory cytokine induction and/or assays previously established in other disciplines (e.g., cosmetic safety testing). As data from unvalidated model systems such as these are gathered and compared with results from established preclinical testing systems (such as the RVI model) and, optimally, from clinical trials, decisions can be made as to the added value from these systems. As clinical trial experience, especially with larger trials, grows, this iterative process is expected to yield more reliable preclinical indicators of probable safety in human trials that, in turn, can provide more effective guidance in prioritizing among multiple potential candidates.

Custom-formulated microbicide candidates with an acceptable score in the RVI test, as defined above, will be considered for NIAID-supported IND-enabling studies (i.e., genotoxicity; absorption, distribution, elimination [ADE]; stability/purity; and condom compatibility) per FDA requirements if there is corporate commitment to advance the candidate into Phase III testing. Examples of commitment are (i) full support for manufacture of sufficient product to support a Phase III study, (ii) agreements to facilitate access by poorer populations in exchange for manufacture, (iii) agreements for technology transfer to developing countries with a specific number of doses negotiated and tiered pricing, or (iv) provision of lots of product shown to be efficacious to communities involved in the testing.

Entry into Clinical Efficacy Trials

Beginning with the NIAID-funded HIV Network for Prevention Trials (HIVNET) and continuing with the HPTN, investigators have established a selection process for determining which candidates would enter into screening or efficacy trials, by enlisting an independent advisory panel that consists of

- An industry representative, from an organization with no microbicide-related product development plans, who has experience in development of topical products
- Two representatives with expertise in preclinical development of pharmaceuticals for infectious diseases, particularly expertise in safety and efficacy testing in animal models
- A virologist with expertise in development of resistance to antiviral drugs
- A regulatory expert
- A DAIDS representative

Periodically, this panel meets in joint session with the HPTN Microbicide Science Working Group to review confidential presentations by microbicide sponsors. Data are reviewed in the context of clinical trials planned through other sources of support such as the Population Council, CONRAD/GMP, Medical Research Council, or UNAIDS, and the subsequent development trajectory for each product is evaluated. Only products supported by a majority of the independent advisory panel are advanced to Phase III testing.

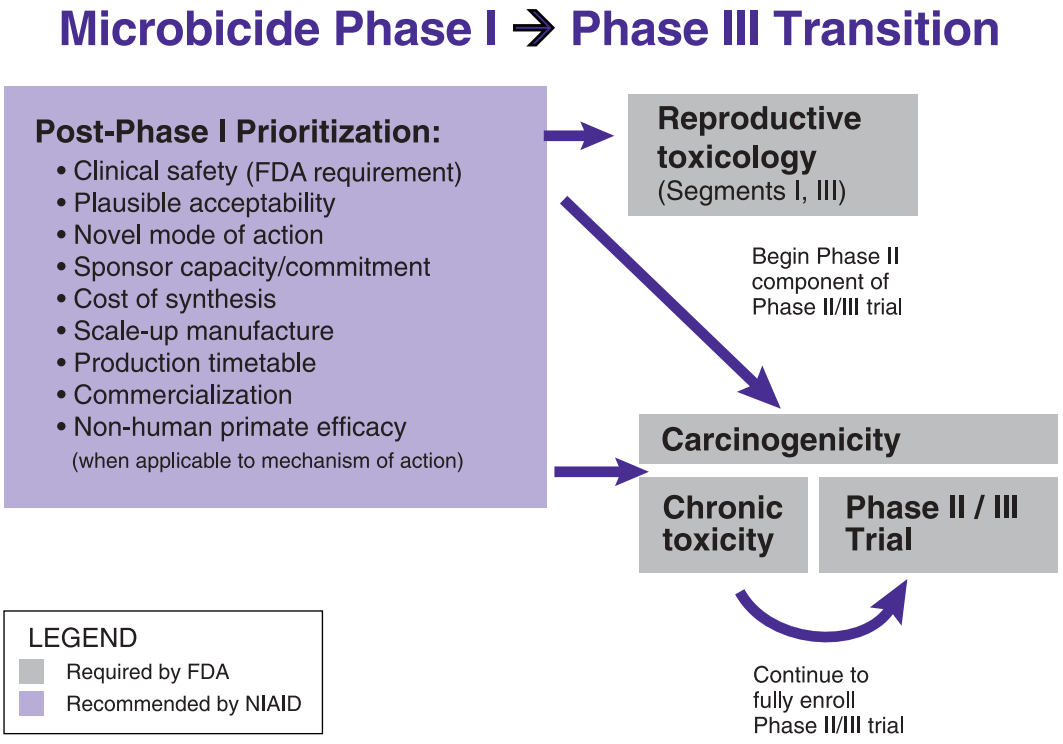
Nonhuman primate efficacy testing is recommended if it is feasible to evaluate the selected microbicide candidate in a nonhuman primate model (i.e., mechanism of action is relevant and activity against the SIV or SHIV to be used in vivo has been confirmed in vitro). Should efficacy studies be conducted in nonhuman primates, interpretation of the results should take into account the constraints imposed by (i) the specific conditions (e.g., progesterone pretreatment and/or single high dose viral exposure) under which the microbicide candidate is tested; and, (ii) the statistical significance of the studies.

To support this decision-making process, microbicide candidates currently undergoing Phase I testing in humans will be given priority in an NIAID-supported nonhuman primate model. Comparative primate trials to compare preclinical efficacy are not contemplated; they require large numbers of animals to perform and are uncertain indicators of relative clinical efficacy. On the other hand, favorable findings in a nonhuman primate model would be considered as supportive evidence in favor of advancing a product into efficacy trials. At the conclusion of a Phase III trial, it may also be possible to evaluate the utility of nonhuman primate models for predicting efficacy in humans.

From a practical perspective, it is important to recognize that in addition to considerations of safety, effectiveness, and acceptability, product development involves a complex array of developmental steps related to preclinical testing, early clinical evaluation, practical considerations of scale-up manufacture, stability, and sponsor support. As a result, the products available to advance into effectiveness trials at any given point in time may be a result of a set of unforeseeable contingencies, such as having been subject to fewer delays or setbacks that cause otherwise equally plausible products to be at an earlier stage of development. Accordingly, alongside the specific comparative preclinical characteristics of candidate products, the advancement of suitably qualified candidates into effectiveness trials may also take into account such practical considerations as clinical trial capacity, product availability, the overall microbicide pipeline, timeline for development, and potential for future formulation as part of a synergistic combination.

Where multiple products representing a similar mode of action and/or chemical composition have reached the same stage of preparedness to enter effectiveness trials, and absent compelling bases for distinguishing among them with regard to likely clinical safety and effectiveness, intermediate-sized or screening trials may be considered as a way to select the most promising candidate to advance into definitive trials.

Thus far, NIAID's clinical evaluation capacity within the HPTN – in the context of clinical trial plans supported by other organizations – has been sufficient to advance those products for which an IND has been filed and for which sufficient quantities are available or can be produced to support Phase I testing.



NIAID Topical Microbicide Program – 5-Year Scientific Priorities

NIAID-supported research and development over the next 5 years is expected to emphasize the following scientific goals in basic research, preclinical product development, and clinical testing.

Basic Research

- Develop and refine in vitro and in vivo models to aid in the identification of microbicides active against HIV and other STI pathogens, as needed
- Explore novel approaches to prevention of infections while improving safety profiles
- Stimulate formulation research to understand the characteristics of individual formulation components that lead to formulations that are safe and acceptable
- Continue to facilitate efforts to understand the similarities/differences in the factors associated with cervicovaginal and anorectal HIV transmission relevant to microbicide discovery and development

Preclinical Product Development

- Facilitate partnerships between academia and industry focused on product development through outreach to developers of candidate agents and potential sponsors
- Ensure advancement of promising candidates through milestone-driven development plans
- Evaluate microbicide formulations in animal models through partnership agreements
- Compare preclinical results – from in vitro, ex vivo tissue-based, and in vivo animal model systems for evaluating microbicide safety and efficacy – with clinical results, to understand the predictive value of the models individually and collectively. If necessary, refine the existing models or develop improved models
- Assess anti-STI activity of microbicides developed to inhibit HIV transmission
- Evaluate – as a follow-up to an initial June 2001 workshop on rectal microbicide research and development – important considerations for developing and qualifying products to protect against rectal sexual transmission

Clinical Trials

- Maintain core capacity of specialized domestic and international clinical trial sites for the conduct of Phase I and Phase II topical microbicide trials
- Identify, develop, and qualify additional efficacy and effectiveness trial sites in developing country settings that offer appropriate populations for Phase III trials – including community-randomized trials – of new candidate microbicides
- Explore partnerships with other agencies with expertise and capacity in surveillance (e.g., CDC) to evaluate long-term safety

Part B:

Microbicide Development: Opportunity and Scientific Challenges

Scientific Challenges of Microbicide Development

With 42 million people infected, predominantly through sexual intercourse, and including 19.2 million women, additional strategies are needed to prevent sexual transmission of HIV and of other STIs that may increase susceptibility to HIV and cause substantial morbidity in their own right. A consensus has emerged that safe, effective, accessible topical microbicides – foams, gels, creams, suppositories, etc. – applied intravaginally or intrarectally to block HIV or other STIs would be a useful tool to prevent new infections.

The long-term goal of NIAID is to identify safe and effective microbicides against HIV/AIDS and other STIs. NIAID's nearer-term goal is establishing proof-of-concept (i.e., safety and effectiveness) of at least one candidate microbicide against HIV/AIDS. Once this proof-of-concept has been established, NIAID's focus will shift to product optimization in relation to the broad criteria listed in Part A, Table 1, for an ideal product.

To achieve this goal, NIAID supports an integrated extramural microbicide program consisting of three complementary components.

- Basic science as the foundation for discovery and development of innovative approaches, novel protective mechanisms, and improved preclinical evaluation tools
- Preclinical to clinical translational research
- Clinical trials

After a brief overview of the principal challenges in these stages of the research and development process, this document reviews the overall scientific rationale for microbicide development, then elaborates on key scientific issues and opportunities in each of the three areas in greater detail.

The discussion below is framed in terms of HIV, which remains NIAID's highest priority for topical microbicide development,[17] although many considerations associated with development of products to protect against HIV infection pertain also to other STIs, and a microbicide effective against multiple STIs remains the eventual goal.

Basic Science for Discovery of New Agents and Improved Tools

Microbicide discovery has paralleled, but lagged behind, HIV drug discovery. Until several years ago, microbicide discovery was somewhat opportunistic, a byproduct of screening large panels of available agents for potential activity against HIV. In addition, surfactants were considered a source of potential candidates because in general they were expected to be capable of disrupting the viral envelope. However, the readily identifiable and easily testable agents that have so far emerged from this high throughput screening approach have been limited in two ways. First, the screens were limited to only a few distinct modes of action. Second, some of these mechanisms – particularly membrane disruption or non-specific blocking of receptor sites – raise important concerns about potential toxicity.

More recently, however, the concept of combination therapeutics – elucidating distinct stages of the HIV life cycle (specifically viral attachment, intracellular penetration, and cell-to-cell dissemination) and then simultaneously blocking multiple distinct stages – has been applied to microbicide discovery and development. Many now appreciate that the most effective microbicides probably will employ combinations of agents that block separate and distinct stages in the processes that permit initial HIV acquisition

and subsequent dissemination to susceptible target cells. In turn, microbicide discovery increasingly emphasizes a detailed understanding of each step of the process of initial infection and subsequent dissemination of virus. As a result, current scientific priorities include unraveling the cellular and molecular processes involved in HIV and STI infection at mucosal surfaces, as well as elucidating natural protective mechanisms in the vaginal vault and anorectal canal.

Translational Research and Product Development

Translational research – from bench to clinic and clinic to bench – is intended to be an iterative process in which pilot clinical findings associated with safety, putative efficacy, or acceptability in turn guide further modifications of candidate agents or formulations. The types of studies performed during this iterative process to qualify, prioritize, and if possible, optimize microbicides for clinical testing have increased in number and complexity, moving from reliance on relatively simplistic in vitro assays and generic toxicity screens used for any drug or biological agent to increasingly sophisticated models designed to more closely approximate the molecular and physiological characteristics of HIV transmission and infection in humans.

Two major considerations have motivated this transition. First, safety is paramount, particularly for a product that higher risk individuals will need to use at least daily for long periods of time. Conventional toxicity screens have been inadequate to accurately gauge the risk of products that have entered into human trials, so more meaningful indicators of toxicity must be developed. Likewise, simple in vitro assays of HIV-killing by a potential agent provide little predictive power for efficacy when formulated and evaluated in vivo. Further, no available ex vivo or animal model captures all potentially relevant features of sexual transmission in humans. To address the limited applicability of any single animal model, multiple models are being utilized with the expectation that one or more of these, separately or in combination, may provide a meaningful preclinical assessment of product toxicity and/or efficacy.

With increasingly detailed knowledge of the basic biology of mucosal HIV transmission, development and utilization of multiple and more sophisticated in vitro testing systems, ex vivo models, and animal models has become a priority. But all animal models remain imperfect analogues for sexual transmission among humans. Multiple models already are available, each with its own apparent limitations, and efforts continue in developing models that balance competing priorities, such as mimicking as specifically as possible the specific conditions of sexual transmission and infection in humans and minimizing the number of animals required to conduct any single experiment. Such model elaboration will continue until efficacy trials provide a means for selecting model(s) that seem to provide the most meaningful insight into likely safety and potential efficacy.

In addition to a greater diversity of preclinical ex vivo and animal models, loss of mucosal infectivity of challenge stocks over extended periods of time (e.g., 3 to 4 years) require that the potency of the challenge stock must be well established prior to

A consensus has emerged that safe, effective, accessible topical microbicides – foams, gels, creams, suppositories, etc. – applied intravaginally or intrarectally to block HIV or other STIs would be a useful tool to prevent new infections.

any experiment in order to assure that infection will occur at the anticipated rate among controls and that experiments conducted at different points in time can be meaningfully compared. Also, the number of promising products has overwhelmed current capacity to conduct comparative studies in nonhuman primates.

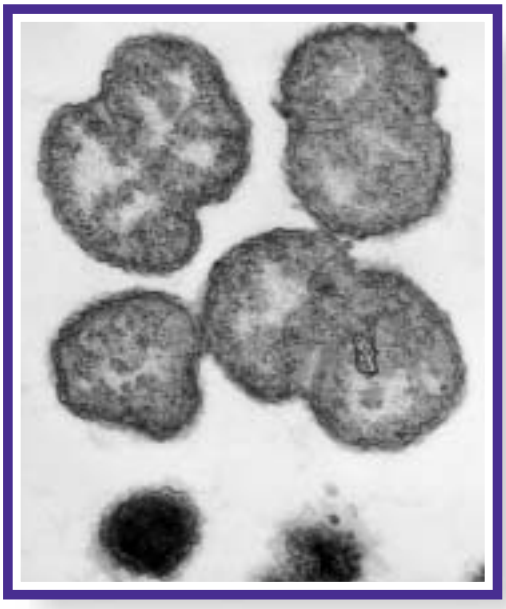
Clinical Trials

An increasing number of plausible candidate agents are making their way through the preclinical development pipeline. Comparative results from sufficiently powered animal model efficacy studies would help prioritize candidates, especially those from the same class or representing a common mode of action. Until efficacy in human trials has been measured, however, the validity of all such animal models will remain uncertain. Although a single animal model with good predictive value would provide useful guidance during product selection and prioritization, ultimately only human efficacy trials can provide a definitive measure of efficacy.

Second, sample size requirements for efficacy/effectiveness trials have grown. The most appropriate target population for the bulk of trial enrollees is women whose risk results from moderate frequencies of sexual contact with a spouse or with one or few sexual partners: the same women who are likely to represent the largest group of users of a licensed microbicide. However, evaluation solely among women whose risk is moderate may underestimate safety concerns for women of higher risk. In contrast, microbicide efficacy trials that recruit preferentially among the highest incidence populations of women – sex workers having many partners and many episodes per day of sexual contact – would require fewer volunteers, but overestimate safety concerns for most eventual users.

In either case, the large sample sizes for efficacy trials virtually mandate multi-country efficacy/effectiveness trials. Other considerations also motivate multi-national trials. The effectiveness of a microbicide will depend on both its biological efficacy when used perfectly and its acceptability, which is likely to affect adherence to guidelines for product application. Given the likely significance of cultural factors for product acceptability, field trials should be conducted concurrently in multiple countries to provide useful comparative data.

Although the breadth of research challenges may seem daunting, investment in microbicide research and development is well justified, as discussed below, by the limitations of existing approaches to prevention of sexual transmission of HIV, together with various lines of evidence suggesting such an approach is fully plausible and feasible. Complementing investments by NIAID, other governmental and non-governmental organizations continue to expand their commitment to this effort, and new organizational entities are being established with the intent of addressing specific gaps in, or otherwise facilitating, microbicide development.



Microbicide Research and Development: Scientific Opportunity and Response

Limitations of Existing Strategies to Avert Sexual Transmission of HIV

Currently available mechanical and chemical barriers used to present HIV transmission have many limitations. The male condom, when used consistently and correctly, effectively blocks transmission of HIV and gonorrhea, although it has a limited spectrum of efficacy for other STIs. Importantly, the condom requires active cooperation of the male partner and therefore cannot be implemented at the independent discretion of the female. The female condom requires partner acceptance, as well as correct insertion and proper use. Also, studies have yet to establish its efficacy in preventing viral and bacterial STIs.

Attempting abstinence or seeking male partners' cooperation in using condoms is unrealistic under circumstances of non-consensual sex.Nor is negotiating condom use a reliable strategy in the context of consensual sex with a partner whose risky sexual practices may remain undisclosed. Conversely, just as oral contraceptives dramatically enhanced the ability of women of childbearing age to avoid unwanted pregnancy, effective, female-controlled topical microbicides would empower women of all ages – including older, post-menopausal women and adolescents – to avoid STIs.

Although bacterial STIs can be treated effectively and relatively inexpensively in countries where antibiotics are readily accessible, these infections often remain asymptomatic in women and difficult to diagnose without appropriate laboratory facilities. As a result, they may go untreated – especially in settings with underdeveloped health care infrastructures – with outcomes ranging from pelvic inflammatory disease through infertility and miscarriage. Infection by viral STIs such as genital herpes and human papilloma virus (HPV) cannot currently be eradicated once acquired. Suppressive therapy against HSV is costly and cumbersome. HPV – as a causal agent of cervical cancer – is associated with very high costs for diagnosis and treatment of dysplasia or more advanced disease.

In the absence of a safe and completely effective HIV vaccine, additional strategies to prevent sexual transmission of HIV are among the highest priorities for prevention research. Even if a partially effective vaccine were available, supplementary methods against HIV, as well as agents with broad-spectrum activity against multiple STIs, could confer additional protection during and after immunization.

The Potential for Topical Microbicides

The goal of NIAID's microbicide research program is to identify safe topical microbicides effective against sexual transmission of HIV and other STIs. Notwithstanding the potential benefit of topical microbicides active against multiple STIs, development of a safe and effective microbicide with activity against any single sexually transmitted pathogen would represent a seminal achievement by

- Reducing morbidity and/or mortality
- Improving insight into common fundamental aspects of microbicide development, such as formulation, clinical trial design, and acceptability

- Stimulating additional investment in product development and optimization, and in methods of deployment to at-risk populations In addition to protecting women from HIV- and STI-related morbidity and mortality, microbicides could indirectly safeguard infants. Preventing HIV infection among women in turn eliminates the risk of transmission to infants during pregnancy, delivery, and breastfeeding. Sparing women the burden of other STIs in turn prevents neonatal infections with gonococcal and chlamydial conjunctivitis that may lead to congenitally acquired blindness or chlamydial pneumonia, a source of chronic respiratory disease; congenitally acquired syphilis; and neonatal herpes.

Plausibility of Topical Microbicides

Ample precedents exist to suggest the plausibility of topical agents for protecting against vaginal and rectal infection with HIV and other STIs.

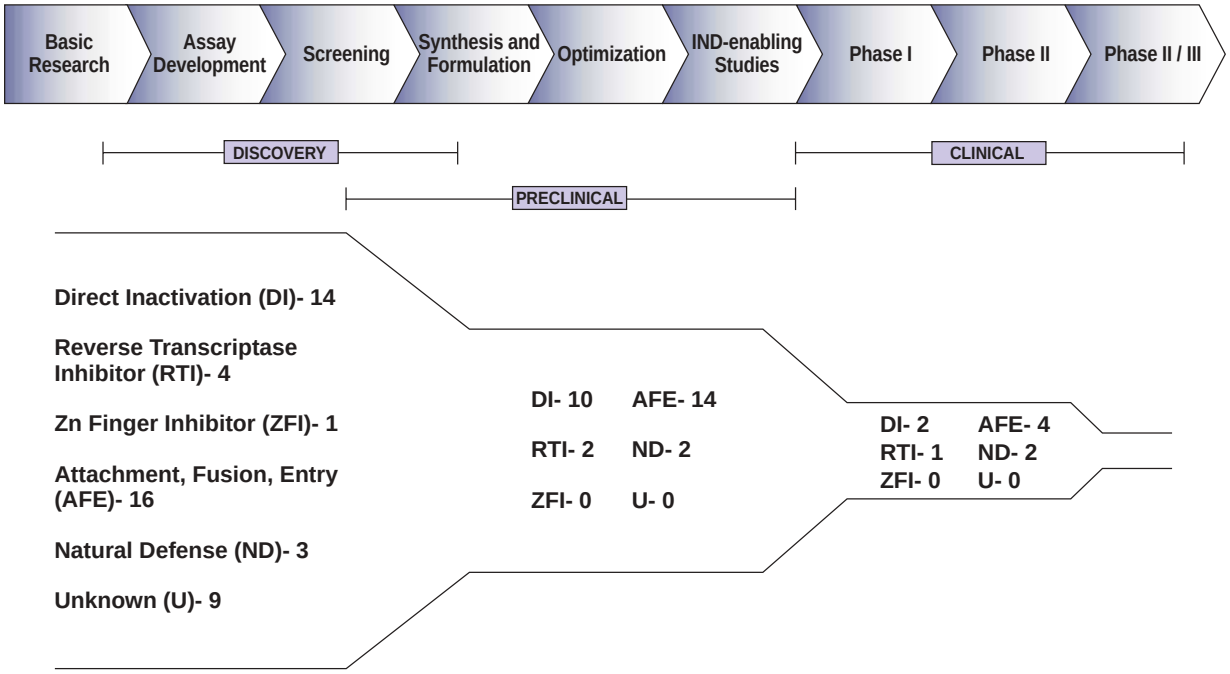
- Over-the-counter topically applied antifungals have been approved for treating vulvovaginal candidiasis (moniliasis).
- Mouth rinses containing antiseptics such as chlorhexidine gluconate or pvp-iodine have been shown to reduce bacterial-associated plaque accumulation.
- Topical vaginal estrogen has been used successfully to treat atrophic vaginitis caused by estrogen deficiency in post-menopausal women and is particularly effective because it avoids the adverse consequences observed with systemic estrogen therapy, including endometrial hypertrophy and suppression of ovarian function.
- The achievement of protection against mucosal challenge, with high-titer virus, in animal models – admittedly an imperfect analog for sexual transmission among humans – nevertheless lends credibility to the concept of protection by a topically applied product.
- Observational and quasi-experimental studies estimate a failure rate of only about 20 percent among "typical" couples for vaginally applied spermicides in the form of foams, creams, gels, jellies, suppositories and vaginal film; randomized controlled clinical trials of such products are only now in progress. Given the high "susceptibility" to pregnancy during the period of ovulation, this overall level of contraceptive effectiveness is highly suggestive of the potential of topical microbicides to prevent transmission of HIV and other STIs.
- Promising safety profiles in early phase trials of new microbicidal agents, together with high rates of self-reported microbicide use among high-risk women participants in previous N-9 efficacy trials, lay encouraging foundations for proof-of-concept trials of the efficacy of new products.

Progress to Date

Progress in microbicide development can be measured by the entry and movement of products through the development pipeline and – perhaps more importantly – advances in basic, preclinical, and clinical science that have broadened and deepened the scientific foundations for rational product development and evaluation.

Approximately 50 to 60 distinct agents that show some promise as potential topical microbicides have been identified.

Figure 1. Microbicide Pipeline



The Pipeline

Approximately 50 to 60 distinct agents that show some promise as potential topical microbicides have been identified (Figure 1). A large proportion of these candidates cluster within a small group of distinct chemical classes (e.g., sulfated and sulfonated polymers). The majority of candidates have yet to progress through the comprehensive preclinical studies required prior to clinical trials. Thus far, relatively few microbicide candidates have successfully qualified to enter clinical testing, and only those products containing the detergent compound N-9 have advanced to efficacy trials. N-9 acts by disrupting the lipid bilayers of enveloped viruses, including HIV, as well as the cellular membranes of sperm. However, this mode of action is non-specific and potentially disruptive of normal cell membranes. Indeed, results from Phase III trials of N-9-containing products have been disappointing. In the vaginal formulations evaluated to date, N-9 does not provide significant protection against sexual transmission of HIV. Furthermore, mucosal erosions and lesions have been detected among high frequency users. Also, a recent study documented shedding of rectal epithelial tissue within minutes of applying over-the-counter lubricants containing relatively low concentrations of N-9.[18]

However, it would be inappropriate to over-generalize from the disappointing results of N-9 studies. This compound entered trials because it was readily available in multiple formulations as a spermicide and because it showed substantial virucidal activity using simple in vitro models of HIV inactivation. Absence of protection has several possible implications

- With a narrow therapeutic window between host toxicity and antimicrobial activity, the detergent may erode vaginal and/or cervical epithelial cell membranes with frequent use, thus permitting direct entry of intact HIV to

the bloodstream should free or cell-associated viral particles escape complete disruption. Intermittent or inconsistent users of microbicides and condoms might have been at increased risk of exposure to HIV at the sites of such erosions.

- N-9 activity in vitro may not predict in vivo clinical activity.
- Commercially available topical N-9 formulations may have been inappropriate, either insufficiently masking toxicity or else delivering subtherapeutic doses of N-9.

Although the concept of conferring protection using a topical agent thus remains unproven in humans, we have learned that definitive clinical trials of such products are feasible and achievable. They can be conducted successfully among diverse populations of women at risk, during which participants willingly use such products in the context of sexual intercourse. There remains, therefore, great potential to succeed through developing new agents formulated specifically for this purpose.

Recent Progress in Basic, Preclinical, and Clinical Science

Studies fully or partially supported by the NIAID topical microbicide program in basic, preclinical, and clinical microbicide research and development have contributed to an improved understanding of both the challenges and the opportunities associated with microbicide development.

- Basic research projects have elucidated several specific mechanisms and pathways through which sexual transmission of HIV occurs, thereby identifying potential new targets for intervention.
- Preclinical efforts – particularly in developing and utilizing nonhuman primate models to gain increased insight into potential human safety and efficacy – have focused on improving the fidelity of existing assays and methods to the known physiological characteristics of the human vagina and processes of sexual transmission. However, dynamic processes of intercourse and their impact on such preclinical measurements remain important considerations. Particularly for nonhuman primate models used to assess potential efficacy, continued model refinement, and further model development if necessary, would increase the perceived relevance of such outcomes to decisions on whether to advance products in expanded human trials.
- Clinical research has moved the first generation of non-detergent microbicide candidates to a stage where they are poised to enter efficacy trials. The availability of a variety of candidates for efficacy trials – difficult to prioritize for advancement because of the absence of dramatic differences in preclinical findings – does not appear problematic for the immediate future. As additional candidates representing multiple modes of action proceed through preclinical development, however, more sensitive ways to establish priorities among candidates will become essential, given the limitations on global efficacy trial capacity. Expansion of efficacy trial capacity will remain a critical need, however, even after establishing more rigorous thresholds for the advancement of products into large field trials.

Some of the many important findings associated with current concepts of HIV transmission and pathogenesis have significant implications for targeted development of novel microbicides.

Basic Research

Some of the many important findings associated with current concepts of HIV transmission and pathogenesis have significant implications for targeted development of novel microbicides.

HIV Co-receptor Expression, Genetic Variations, and Risk of Transmission

Additional potential targets for development of vaccines and anti-HIV agents, including microbicides, have been identified in the course of basic research on the molecular mechanism of viral attachment to and entry into susceptible cells. It is now known that HIV infection of target cells requires both the primary CD4 receptor and either of two co-receptors, CXCR4 or CCR5. The physical interaction of CCR5 and CD4 in the cell membrane must remain undisturbed in order for HIV to enter the cell. Pharmacologic modification of the CCR5-CD4 interaction could offer a strategy for specifically blocking HIV entry.

Studies of a unique variant HIV IIIBx have demonstrated CXCR4-dependent infection of CD4 cells, suggesting the potential to block infection by preventing interaction between CCR5/CXCR4 and gp120 envelope. Therapeutic or microbicidal agents might employ small molecules that block the active sites of these interactions. Or a vaccine might be formulated from a suitably presented antigen that elicited antibody specific to the active site.[19]

Continuing population-based research on the distribution of gene variants associated with CCR5 has extended the initial finding of a protective effect of distinct genotypes. A specific CCR5 marker associated with greater susceptibility to infection has also been shown to predict more rapid disease progression following infection. On the other hand, a genetic marker associated with a particular RANTES variation predicts a greater risk of acquiring HIV and more rapid disease progression if infected among Europeans but the same variant has no such modifying effect in disease progression among HIV-positive African Americans.[20] Further elucidation and characterization of the molecular and functional differences associated with these genetic and structural variants may lead to new insights into modes of protection from infection and dissemination of viral particles from initial target cells.

Prevention of Vaginal Transmission of SIV by Estrogen

Epidemiologic research initially suggested, and continues to investigate, a mechanism that also has been demonstrated in simian experiments showing that hormonal factors very likely modify susceptibility to HIV infection. Furthermore, this mechanism appears to be mediated by the effect of hormones on the thickness of the vaginal epithelium. These studies have facilitated the development of a laboratory model for looking at the efficacy of experimental microbicides on protection against pathogenic strains of SIV. Also, although a variety of potential routes of mucosal infection during vaginal exposure have been established in in vitro and ex vivo studies, these findings suggest that models of the relative importance of different potential routes of exposure and infection should consider as salient the integrity of the vaginal epithelium.

In observational studies, women whose estrogen levels have been depressed by treatment with the contraceptive depo-medroxyprogesterone acetate (DMPA) have an increased risk of HIV infection. This association is consistent with estrogen's role in stimulating thickened vaginal mucosa. After ovariectomized female macaques received no

hormonal treatment, progesterone, or estrogen, untreated control and progesterone-treated macaques (11/12) became infected while none of the 6 estrogen-treated macaques were infected. The association between blocking of HIV infection by estrogen-thickened vaginal mucosa was further supported by the successful infection of the estrogen-treated macaques with a subepithelial inoculation of HIV.[21] Progesterone pre-treatment has since been found to increase the sensitivity and efficiency of nonhuman primate efficacy models by assuring that all control animals become infected. Topical estrogen also has been suggested as a possible ingredient for a vaginal microbicide. More generally, these studies support an emphasis on the compatability of candidate microbicides with the maintenance of intact vaginal epithelium.

A Novel Protein (DC-SIGN) on Dendritic Cells Delivers HIV to T Cells.

One of the newest potential targets for microbicide development has been identified during detailed examination of the behavior of a type of immune cell known as a dendritic cell in its response to HIV. Studies of this cell type have revealed what may be an important mechanism for conveying HIV from the initial site of exposure to large internal reservoirs of susceptible CD4 and other immune cells.

Dendritic cells were of interest because they appear to play the role of sentry in their immune system role of patrolling skin and mucosal surfaces such as the rectum, vagina, and cervix; identifying, capturing, digesting, and displaying fragments of foreign invaders, such as microorganisms; and thereby alerting other immune system cells, such as T cells to mobilize. Studies of the effector molecule on the dendritic cell surface, DC-SIGN, revealed multiple projections that bind to HIV but do not inactivate it. Thus, DC-SIGN delivers HIV particles to CD4+T cells that retain infectivity for long periods, resulting in efficient virus infection and replication. Because of its important potential role in facilitating HIV dissemination from initial target cells, as well as its potential role in mediating HIV infections despite intact epithelium, DC-SIGN is a potential target for vaccines, therapeutics, and microbicide development.[22]

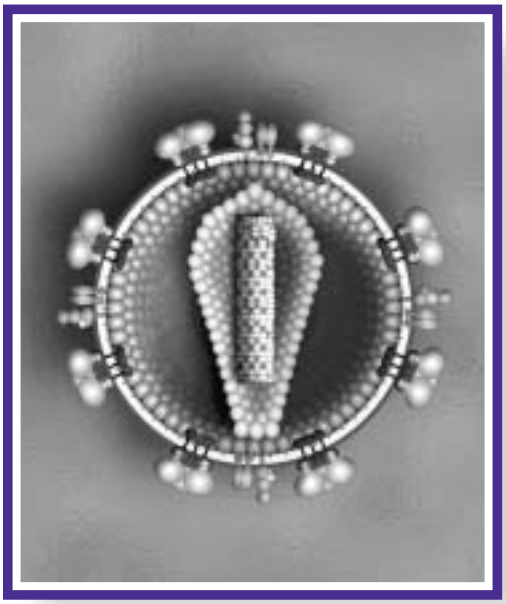
HIV-1 Buds from Specialized Regions of Host Cell Membrane.

As suggested previously, significant work has focused on the mechanisms of HIV attachment and infection of susceptible cell types. At the other end of the HIV life cycle – the final assembly and expulsion of new virions from host cells – new findings with potential for exploitation in microbicide development have emerged.

Increased understanding of the process of HIV budding has identified a specific cell structure associated with this final stage of HIV replication. As HIV-1 buds from the cell, it selectively incorporates lipids localized in specialized regions of the host cell membrane known as glycolipid-enriched membrane (GEM) domains or lipid rafts – organized areas on the cell surface enriched in cholesterol, sphingolipids, and glycosylphosphatidylinol (GPI)-linked proteins.[23] Further elucidating mechanisms of HIV assembly and the role of host constituents in the HIV-1 life cycle may have implications in developing agents with microbicidal properties.

Preclinical Product Development

In vitro models utilized during comparative preclinical evaluation of microbicide candidates increasingly reflect the natural characteristics of



human vaginal ecology (e.g., the antiviral and antibacterial effect of colonization by two strains of peroxidase-producing *Lactobacillus*), the nature of the infectious unit (cell-associated or cell-free virus), distinct potential routes of infection (CD4-dependent and CD4-independent), and the physiologic characteristics of mucosa at different times during the menstrual cycle. The most recent addition to the battery used to screen and prioritize compounds with potential microbicidal efficacy is a CD4-independent assay effective over the normal, acidic pH range of the healthy female vagina (4.5 to 7.4).

Multiple nonhuman primate models have contributed suggestive findings regarding both safety and efficacy. The pigtailed macaque has been used to assess safety (effects on surface tissues and microenvironment of the cervix and vagina) of 14 candidate agents. In general, too few animals have been used to be able to quantify protective efficacy or achieve high levels of statistically significant protection, because scarcity, technical feasibility, and expense have so far discouraged nonhuman primate studies with numbers sufficiently large to achieve such increased levels of precision.

- Three doses of PRO2000[24] (applied vaginally 15 minutes prior to viral challenge) were compared for efficacy with saline control in protecting female adult macaques from infection with 10 animal infectious units of SHIV 89.6PD. All controls (i.e., 7 of 7 animals) became infected within 2 weeks of challenge. Only 1 of 7 animals became infected in each of the 4 percent and 2 percent groups while 0.5 percent PRO2000 provided complete protection from infection in 7 of 7 animals.[25]

- Over-the-counter, commercially available bioadhesive gels with 3.5 percent N-9 (Advantage 24) or without N-9 (Replens) were applied topically to adult female rhesus monkeys 15 minutes prior to intravaginal challenge with SIV. Four of five monkeys in the untreated control group became infected after a single inoculation. Advantage 24 protected four of five monkeys from infection. Replens prevented infection in two out of five monkeys,[26] implying that a physical barrier alone may confer partial protective efficacy.

- Concurrent with its early clinical evaluation as a therapeutic agent, PMPA,[27] formulated as a gel, was administered to adult female rhesus monkeys in different concentrations and time intervals prior to SIV exposure. PMPA gel prevented vaginal acquisition of SIV infection when administered pre- and post-exposure in multiple applications, or as a single application administered 15 minutes prior to viral exposure.[28]

- Three candidate microbicides have been evaluated for efficacy against chlamydial challenge in a pigtailed macaque model. Several of these microbicides are advancing into initial safety or efficacy testing in human trials.

Figure 2. NIAID-Supported Microbicide Clinical Trials

Microbicide Candidate	Clinical Trial	Status
Advantage 24	Phase I (rectal)	Complete
BufferGel	Phase I (vaginal)	Complete
PRO2000/5 Gel (P)	Phase I (vaginal)	Complete
Carraguard	Phase II (vaginal)	Data analysis ongoing
BufferGel	Phase I (penile)	Complete
PRO2000/5 Gel (P)	Phase I (penile)	Complete
Tenofovir Gel	Phase I (vaginal)	In progress
Cellulose Sulfate Gel	Phase I (vaginal/HIV^{+})	In progress
PRO2000/5 Gel (P)	Phase I — India (vaginal)	In progress
PRO2000/5 Gel (P)	Phase II/IIb (vaginal)	Q2 2004
BufferGel	Phase II/IIb (vaginal)	Q2 2004

Clinical Trials

Principally through its multi-center HIV prevention trial networks – previously the HIVNET and currently the HPTN – and also through investigator-initiated grants, NIAID has funded early Phase I safety and initial acceptability assessments of a variety of new microbicide candidates, as described below and summarized in Figure 2.

- PRO2000 (at concentrations of 2 percent and 4 percent administered once or twice daily) was given to sexually active HIV-negative and abstinent HIV-positive women at 2 U.S. and South African sites during 14 consecutive days. During this relatively brief period of product exposure and use, it was well tolerated by both the HIV negative and HIV positive women, with no serious adverse events. Adverse event rates were not significantly associated with either HIV status or exposure variables such as concentration or frequency of use. All of the women indicated they would be willing to use the product again if it were shown to protect against HIV infection.[29]
- BufferGel, a non-detergent microbicide, is expected to maintain normal, acidic vaginal pH in the presence of semen, and thereby inactivate HIV and other STI pathogens. Results of a Phase I trial of low-risk women in the United States showed that BufferGel was non-toxic and well tolerated. A comparison of responses to questionnaires on hypothetical pre-trial predictors of acceptability indicated that actual experience with the study product, rather than attitudes prior to use, was associated with willingness to use such products in the future, suggesting that strategies encouraging women to try unfamiliar products are more likely to achieve acceptance than educational campaigns designed to change pre-existing attitudes.[30]

  An expanded Phase I trial was then conducted to examine the safety, acceptability, and use of BufferGel in India, Thailand, Malawi, and Zimbabwe. About half of the women in

the study, both sexually abstinent and sexually active, reported at least one adverse event (AE) that could not be attributed to some definitive non-product related etiology. All AEs were mild or moderate (none were serious) and virtually all resolved during or soon after the trial. Among all centers in the multi-national trial, compliance with product use guidelines (twice daily for 14 days) was high, as was overall acceptability, except in India.[31]

- A randomized, placebo-controlled Phase I/II trial to assess the safety and acceptability of Carraguard, a lambda-carrageenan (PC515) non-contraceptive sulfated polysaccharide microbicide, has completed enrollment at several sites in South Africa. Data analysis is ongoing.
- Despite the widespread presence of N-9 in commercial sexual lubricants used by U.S. men who have sex with men (MSM), high doses or prolonged, frequent exposure may cause tissue damage that in turn may increase susceptibility to HIV infection.

To begin to evaluate effects of N-9 on rectal tissue, while examining an applicator-administered intrarectal gel for its acceptability among MSM, Advantage S (52.5 mg N-9 per applicator) was given to 25 HIV-negative and 10 HIV-positive seroconcordant monogamous male couples, who were instructed to insert from 1 to 4 applicators of the N-9 (52.5 mg) gel daily. Safety assessments included genital exam and urine leucocyte-esterase for insertive partners. Receptive partners underwent anoscopy with colposcopy, rectal biopsies, and mucosal samples for semi-quantitative assays of HPV DNA, and in HIV-infected men, quantitative HIV RNA PCR and HSV DNA PCR, before and after product use. Daily use of this formulation of N-9 gel resulted in minimal irritation at the time of the clinical examinations (a minimum of at least several hours after exposure).[32]

Scientific Progress in Microbicide Development Can be Accelerated at All Phases: Discovery, Preclinical Development, and Clinical Evaluation

Scientific progress in microbicide research has increased our understanding of the challenges of developing and establishing the safety and efficacy of promising candidates. However, improved scientific understanding also expands opportunities. For example, a more sophisticated understanding of the biology of HIV infection suggests new potential blocking mechanisms. A richer appreciation of the complexity of vaginal physiology can support more meaningful models for preclinical evaluation and suggest additional clinical markers of toxicity or tolerability. This section further elaborates these challenges and opportunities.

Basic Biomedical Research: Expanding Knowledge of Fundamental Mechanisms of HIV/STD Mucosal Transmission and of Protection From Sexual Infection

With limited understanding of the mechanisms of mucosal HIV/STI infection, to screen compounds for potential microbicidal activity, researchers initially adopted methods used previously to screen candidate agents in such related fields as contraceptive research and HIV therapeutic drug development. In vitro cell-based assays for establishing anti-HIV activity and cytotoxicity, as well as standard animal models to study chemical vaginal irritation and systemic toxicity, have constituted the preclinical discovery and development paradigm for microbicides.

In vitro screening of uncharacterized chemical entities has focused on cell-to-cell and cell-free transmission of HIV-1, although the relative importance of cell-free and/or cell-associated HIV in sexual transmission remains unresolved. Recent progress in fundamental research on mechanisms of infection suggests a broader range of potential blocking strategies. Continued elucidation of the specific mechanisms of mucosal HIV infection during sexual transmission – characteristics of both pathogen and host, including natural host defenses – also might provide a basis for development of methods and models that can improve the sensitivity and specificity of the preclinical screening process. On the pathogen side, ejaculates from HIV-infected men may contain both cell-associated and cell-free infectious HIV-1. Consequently, both must be addressed. However, these two presentations of HIV entail different initial steps in infection: (i) entry of cell-free virus via infection or association with macrophages or dendritic cells (DC) in cervicovaginal or rectal epithelium, (ii) viral entry via interaction of cell-associated virus with susceptible target cells in vaginal or rectal lining, and (iii) direct entry of cell-free or cell-associated virus into the bloodstream secondary to trauma.

Although HIV cell entry appears to proceed through a CD4-dependent path in the presence of co-receptors, mounting evidence suggests that CD4-independent entry via co-receptors also may occur. Defining CD4 and co-receptor

Recent progress in fundamental research on mechanisms of infection suggests a broader range of potential blocking strategies.

requirements more precisely for HIV entry in cervicovaginal and rectal mucosal tissue can help clarify the relative significance for achieving protection with agents that are specific to one of these two pathways. DC-SIGN may represent an appropriate target when epithelial disruption occurs.

Alternatively, transepithelial transmission may not require epithelial disruption, given a potential role for Langerhans cells which may extend cellular processes from the submucosa to the intact mucosal surface, where a receptor similar to DC-SIGN may serve as a receptor for HIV. The effect of intercourse on cervicovaginal and rectal physiology – in the presence and absence of STIs associated with enhanced HIV transmission – would help determine the relative contributions of these distinct mechanisms of transmission.

Just as a combination of physical, microbiological, and chemical barriers act synergistically to protect the cervicovaginal mucosal surfaces from infection and injury, similar mechanisms may also protect the lower gastrointestinal tract including the rectal mucosa. Exogenous topical microbicides should not disrupt either natural defense mechanisms or normal physiological processes. Nor should their activity be affected by or interfere with normal physiological processes – such as exudation of cervicovaginal secretions – that occur during sexual arousal. Further elucidating the nature, contributions, and mechanisms of innate defenses would augment the array of potential concepts of protection that could be a focus for development of new candidates. Assays to evaluate the impact of candidate agents and products on these mechanisms will be relevant to both qualifying and comparing new candidates.

Preclinical Development: Improving the Likely Predictive Power of In Vitro, Ex Vivo, and Animal Models for Safety and Efficacy

Because animal models used to assess preclinical efficacy of microbicide candidates do not emulate all aspects of sexual transmission in humans, the relevance of such test systems for intravaginal topical products is being reconsidered. Models for evaluating intrarectal efficacy and safety have recently been developed; these, too, remain limited by inadequate understanding of host and viral factors specifically involved in rectal transmission of HIV. Recent assay development has sought to address two important considerations.

- The environment to which the microbicide is added undergoes wide variations in physicochemical properties across which the agent must retain anti-HIV/STI activity.
- Immortalized cell lines differ from cultures of fresh cells; they have undergone transformation and may prove less relevant than fresh cells with respect to the molecular events in initial infection.

A successful topical microbicide candidate must be stable and active in a dynamic environment. The viscosity of the vaginal mucosa changes during the course of the menstrual cycle, a variable addressed by devising in vitro assays that are conducted in the presence and absence of mucin. Variations in pH have been addressed by a new cellular assay that simulates the pH transition to replace simple stability assessments at pH 4.0 and pH 7.0.

Although immortalized cell lines grown as monolayers are valued for their ease of use in in vitro screens and their ability to be genetically engineered to express relevant viral and bacterial

receptors, these systems do not mimic the specialized mucosal tissue of the female genital tract or the distal gastrointestinal tract in either structure or spectrum of distinct cell types present. Availability of ex vivo and organ culture models utilizing cervicovaginal, rectal, or skin blister biopsies – a putative counterpart for vaginal tissue for studying HIV transmission – may more accurately reflect in vivo conditions. By requiring biopsy material, such ex vivo systems would be costly and time consuming if used for high throughput screening. But limited comparative testing of different candidates using such a system is feasible.

The conventional rabbit vaginal irritation test – a mainstay of preclinical toxicity testing for other vaginally applied products – does not represent either the pH of the healthy human vagina or the mechanical factors that become relevant during coitus. The rabbit vagina is neutral (pH = 6 to 7), although it is not known whether this limits the predictability of results generated by the rabbit vaginal irritation model. Mechanical effects of coitus (e.g., development of microabrasions) on potential irritation are not addressed in this model because the microbicide candidate is deposited atraumatically in the vaginal vault.

In vitro models can estimate adhesion of various preparations to vaginal mucosa; their dispersion, distribution, and retention within the vagina; and the release of active agents to appropriate submucosal cells. However, available models only imperfectly mimic human vaginal physiology and function. The effects of shear forces, especially during intercourse, on viscosity and bioadhesion will be challenging to estimate ex vivo. Little is known, even from in vitro models, about the behavior of products administered intrarectally. Thus, an optimal strategy would include support for improved in vitro and preclinical models that investigate the effect of physiology and function, intercourse, and the presence of semen on microbicide formulations and their behavior in the vagina and rectum. Such model development would be integrated with clinical studies, or substudies integrated into larger field trials, designed to provide data permitting the successive refinement of such models.

Available nonhuman primate models have imperfect reproducibility and uncertain predictability. In humans, multiple exposures to HIV may precede the event that leads to established infection, whereas current nonhuman primate models are designed to require only a single high-dose exposure to the challenge virus to achieve 100 percent infection.

Animal models offer the best source of information about the likely efficacy of a candidate microbicide short of full-scale human efficacy trials. But they do so with many limitations.

- No single model is germane to all potential mechanisms of protective efficacy that

currently are being explored through product development efforts, so there cannot be a single uniform comparative standard.

- The relevance of a particular level of animal protection in a particular model cannot be known until these preclinical findings can be compared with some level of protective efficacy assessed in a human trial.
- No primate model can parallel all salient aspects of human vaginal/cervical biology. For example, the nonhuman primate vagina is normally pH neutral, although the distribution of microflora does parallel the human vaginal environment. Moreover, there currently is no primate model for infection by cell-associated virus, even though this presentation of HIV may be responsible for some portion of sexual transmission of HIV among humans.
- Human infection is believed to result only after multiple exposures; whereas, until very recently, animal models have emphasized a high-dose viral challenge (see below) that can engender infection upon a single exposure. This requires progesterone pretreatment, whereas women appear to be susceptible during all phases of the menstrual cycle. A model that depends on successful infection after a single challenge dose of HIV may be too stringent, or simply not relevant, as a criterion for a microbicide candidate.
- Nonhuman primates, specifically macaques, are not readily infected vaginally by SIV or SHIV chimeras.[33] Moreover, stocks prepared independently from the same virus strain can vary in efficiency of vaginal transmission. Those virus strains/stocks that do infect via the intravaginal route require a dose of virus three to five logs higher than for the intravenous route. These characteristics of macaque models may be viewed as either beneficial or problematic for model development. If mimicking the relatively inefficient HIV transmission process in humans is a priority, then the requirement for multiple exposures makes this characteristic desirable, as long as the algorithm for successful challenge is clear and repeatable, so that control animals will represent true controls because they can reliably be infected. If using as few animals as possible in any given experiment, and getting results as quickly as possible from such experiments are considered priorities, then a control strategy that depends on a multiple low-dose challenge will be less desirable than a challenge stock that can reliably establish infection after a single vaginal challenge.

To address the limitations identified above, in vitro and animal models for screening microbicides continue to be refined, keeping pace with advances in understanding of how cervicovaginal and rectal transmission may occur. Although the models do not comprehensively recapitulate the nature of HIV transmission during sexual intercourse, each model can provide information as to the potential inhibitory and toxicity profile of microbicides under specific biologic conditions.

- Identification of in vitro inhibitory activity against cell-free virus can provide a preliminary foundation for pursuing a microbicide candidate.
- An efficacy evaluation in nonhuman primates based on achieving protection with a single application of microbicide followed by a high dose viral inoculum can provide proof of biologic plausibility under conditions in which host susceptibility is optimized in the absence of cervicovaginal trauma.

A low-dose, multiple exposure challenge model would make an important contribution by allowing models to evaluate persistence of efficacy of a candidate across multiple uses and exposures. A real world microbicide would be subjected to mechanical dispersion, although incorporating this feature instead of relying exclusively on atraumatic deposition of the challenge virus may not be feasible. If it were, such models would help to characterize important considerations regarding formulation as well as preclinical safety. Models that use cell-associated virus as the infecting unit would become a higher priority if it were known that this is the principal vector of infection in human sexual transmission.

The number of nonhuman primates required for preclinical studies of microbicide efficacy will depend on how outcomes of such studies will be used to guide product development. Head-to-head comparison of all potential products is not feasible. Among those candidates for which nonhuman primate efficacy studies are feasible, the selection of a qualitative readout – some versus no protection or a quantitative readout (e.g., more or less than 50 percent of challenged animals resisted infection) will impact sample size. Currently at most seven animals per arm are used to detect some versus no protection. To distinguish quantitively among products (for instance multiple candidates using the same presumptive mode of action) might require twice this number per arm.

Ultimately, the relevance and predictive value of such models for microbicidal efficacy and vaginal/rectal irritation will require comparisons with data from human clinical trials of microbicide candidates that were also evaluated using these preclinical systems. For example, establishing the extent of epithelial disruption that is clinically meaningful – in terms of increasing susceptibility to HIV/STI infection – remains an unmet need to be addressed in future human studies. Multiple models should be employed until it becomes clear which model adequately predicts efficacy in humans.

Phase I Through Phase III Clinical Evaluation: Establishing Sufficient Capacity to Efficiently Advance Meritorious Products into and Through Proof-of-Concept Trials

Worldwide clinical trial capacity for microbicide research has been sufficient to evaluate new products in Phase I testing, and to assess N-9-containing products in efficacy trials. However, to a large extent this reflects the relative paucity of candidates that have completed preclinical and early clinical development (Figure 1).

The Potential Product Pipeline Will Offer Opportunities to Evaluate an Increased Number of Candidates in Phase I Trials in 2 to 3 Years

The advancement of additional agents identified through screening of therapeutic drugs will combine, beginning in 2 to 3 years, with the maturation of microbicide-targeted preclinical research and development programs that are supporting at least a dozen single and combination candidates. Currently, one or two new products per year become available for Phase I trials. This number is expected to more than double by the middle of the decade. These newer agents – many of them representing novel mechanisms of action – may show more promise than the first non-detergent microbicides available in the

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previous several years. For each promising agent, different formulations and doses may merit clinical evaluation, especially if safety, efficacy, and acceptability are pursued for each agent and combinations. For example, a Phase I safety and dose/frequency escalation trial of a single agent in a single formulation would require 400 to 600 women participants. Entering into Phase I trials all promising agents that demonstrate acceptable preclinical safety hurdles and that meet regulatory requirements will likely tax current Phase I capacity, particularly once a large scale trial gets underway at these same clinical sites.

The Number of Promising Candidates for Phase III Trials Will Exceed Clinical Capacity – Already Severely Challenged – by the Middle of the Decade

At this time, it is not clear whether current global capacity to implement efficacy or effectiveness trials can accommodate current demands imposed by a handful of products that qualify based on FDA requirements for preclinical safety and efficacy, plausibility of protection, and in most cases, some evidence of preclinical efficacy in an animal model.

Few U.S. or developing country clinical settings can readily manage trial cohorts larger than 250 to 500 participants, so multisite investigations are a necessity. On the other hand, the benefit of conducting microbicide efficacy trials in multiple countries is that they could provide important comparative insights into the impact of social, cultural, and behavioral factors on the adoption of microbicides once they reach the market.

In addition, to support U.S. licensure, FDA will expect U.S. women at higher risk to be evaluated at least for safety. Given current seroincidence estimates in higher risk women's cohorts – between 1 and 1.5 per hundred person-years – these women will contribute very few endpoints to Phase III trials, although they will contribute to both safety and acceptability objectives. The net effect, however, will be to reduce the overall efficiency of obtaining the quickest possible proof-of-concept or else to increase the cost and complexity of Phase III trials. In all likelihood, U.S. components of Phase III trials or separate bridging studies will be conducted so that the outcomes become available at the same time as efficacy results, so economies cannot be achieved by delaying this aspect of clinical investigation.

A final consideration that may affect the required size of efficacy trial cohorts is the prevalence of rectal intercourse. Vaginal microbicide candidates may or may not be efficacious for rectal use, given the different anatomical, physiological, and immunological properties of susceptible rectal mucosa. They may not even be safe for anorectal exposure, although rectal safety criteria are being developed and rectal safety is likely to become a routine part of early clinical evaluation of microbicide candidates. To the extent that trial participants who become infected were exposed rectally rather than vaginally, this may reduce the sensitivity of the trial to detect protective effects of vaginal microbicides. The extent to which this factor will require still larger sample sizes is not known because data on prevalence of anorectal intercourse in worldwide populations are very limited. However, this behavior has been sufficiently well documented in the relatively few settings where quantitative or qualitative data have been carefully collected to suggest that further studies of the prevalence and predictors of anal sex will help, at a minimum, in planning future microbicide efficacy trials.

Comparative Phase II Trials, Focused on Expanded Safety and Product Acceptability, Can Help Guide Prioritization

The current strategy is to advance from Phase I safety trials directly into Phase III efficacy trials with an expanded safety run-in phase to assess product safety in the higher risk target populations. This approach addresses the need for expanded safety information related to the specific populations within which the product will be tested and among whom it is intended to be used once approved, prior to full-scale Phase III efficacy evaluation.

The current lack of enthusiasm for a separate Phase II evaluation has resulted from the lack of any surrogate for protection, together with the reasonable expectation that incorporating a Phase II run-in to the first period of a planned Phase III trial would increase efficiency and possibly reduce overall costs. However, there are two important areas where stand alone Phase II trials may come to play an important future role in the development process: first, in obtaining expanded safety data, especially among populations with a high proportion of participants who might use such a product several times a day or more; second, in providing comparative information on product acceptability in varied settings.

Although women who may need to use a protective product multiple times per day – such as sex workers – may be a minority of the total potential user population, they remain a very important population for an effective woman-controlled protective method. Differences in the relative safety of different products when used multiple times per day or against the backdrop of higher STI rates may turn out to be the most important factor differentiating otherwise similar products and therefore a useful guide to prioritization for expanded efficacy/effectiveness trials. Also, knowledge of the frequency of use and dose at which concerns arise regarding local toxicity provides a foundation for labeling instructions regarding recommended maximum repeat usages per day or per week.

Similarly, as previous microbicide trials have suggested, women's willingness to use these products consistently and correctly is a major consideration. In the absence of a definitive surrogate of protection, that might serve as a primary outcome measure for Phase II trials, and with preclinical efficacy an imperfect guide to prioritization, acceptability among representative populations of prospective users becomes a paramount consideration and an important outcome to examine in Phase II, especially if multiple products are ready for comparative testing.

Behavioral outcomes associated with adherence and proper use can be assessed in relatively small numbers of women (e.g., 50 to 100) in enough clinical sites to represent the diversity of populations of women being invited to join efficacy trials. The validity of the results will depend on the extent of differential self-selection between women who agree to enroll in such trials and the composition of subsequent large-scale efficacy trial cohorts. Phase II trials offer, simultaneously, operational benefits.

- Training opportunities for additional research staff
- Early indicators of potential problems with enrollment or retention
- Potential to embed comparative evaluations of different approaches to condom promotion counseling and informed consent education
- Opportunity to refine any new procedures related to specimen collection, processing, storage, and/or diagnostic testing

Conclusion

The preceding discussion implies that in each area of microbicide discovery and development the apparent scientific task has become more complex (and, often, correspondingly more costly) as particular challenges at each stage have become clearer. For example:

- As a guide to further product **discovery**, the fundamental biology of sexual transmission across genital and rectal mucosa and the subsequent dissemination among susceptible target cells has come to be seen as a major source of innovation in development of additional candidate agents specifically designed to block well-characterized steps in the infection process.
- Both expanded populations of nonhuman primates and animal models that more closely mimic the circumstances of sexual exposure among humans have emerged as high priorities in improving the guidance provided by **preclinical evaluation** in selecting the most promising products to advance through human trials.
- The scale and complexity of **clinical trials** will increase as the pipeline of qualified candidates and innovative approaches to formulation and delivery diversifies. Sponsors have increasingly appreciated that communities experiencing relatively high HIV incidence among general populations of women are priority populations for microbicide trials because they represent the largest group of anticipated future users. However, these populations often lead to larger sample size requirements than previous approaches, which sought out even higher incidence groups of women such as sex workers.

An improved understanding of some of the important scientific challenges in microbicide discovery and development – although suggesting the need for more diversified or robust efforts in certain areas – also offers the potential to accelerate attainment of NIAID's goal – safe and effective microbicides against HIV/AIDS and other STIs.

The scale and complexity of clinical trials will increase as the pipeline of qualified candidates and innovative approaches to formulation and delivery diversifies.

ATTACHMENT 1	NIAID TOPMIC GROUP MEMBERSHIP					
TITLE	AFFILIATION					
	Division	AIDS			Microbiology & Infectious Diseases	Other
	Program	*Basic Sciences*	*Treatment Research*	*Vaccine & Prevention Research*		
Topical Microbicide Team Leader				PSB[5]		
Program Officer, Immunology		PBRB[1]				
Program Officer/Project Officer Virology/AIDS Reference & Reagent Program		PBRB				
Project Officer, Nonhuman Primate Evaluation		TIB[2]				
Project Officer, Specialized In Vitro Virological Testing		TIB				
Branch Chief		TIB				
Associate Director		OAD[3]				
Project Officer, In Vitro Virological Evaluation			DDCSB[4]			
Project Officer, Formulations/Manufacturing; Pharmacology/Toxicology			DDCSB			
Project Officer, Chemical Resynthesis; NIAID Chemistry Database			DDCSB			
Branch Chief			DDCSB			
Medical Officer				PSB		
Branch Chief				PSB		
Medical Officer					STDB[6]	
Project Officer, STD Clinical Trials Group					STDB	
Branch Chief					STDB	
Project Officer, In Vitro & In Vivo Virological Evaluation					VB[7]	
Virologist/Immunologist						FDA[8]

[1]Pathogenesis & Basic Research Branch
[2]Targeted Interventions Branch
[3]Office of the Associate Director
[4]Drug Development & Clinical Sciences Branch
[5]Prevention Sciences Branch
[6]Sexually Transmitted Diseases Branch
[7]Virology Branch
[8]Food & Drug Administration

End Notes

[1] CDC. *Tracking the Hidden Epidemic – Trends in STDs in the United States*, 2000, p. 1.

[2] CDC. *Tracking the Hidden Epidemic – Trends in STDs in the United States*, 2000, p. 1.

[3] After intravaginal administration of the microbicide for several consecutive days, the vagina, cervix, uterus, and ovaries are examined visually and microscopically for inflammation and any other changes. Each test includes a positive control, permitting comparison of the effect of new agents in the context of the lesions caused by known commercial intravaginal agents. Other controls expose animals only to the vehicle to distinguish between effects caused by the putative active agent. Although nonoxynol-9 showed deleterious changes in this model, it was considered "safe" based on years of human use prior to development of the model. Nevertheless, any model must achieve the best possible correlation with clinical outcome for validation.

[4] The effects of a formulated microbicide candidate on cervicovaginal tissues and microenvironment are measured immediately (30 min.) and 24 hours following each daily application for 4 days. Recovery of tissues and flora is measured within 1 week of the final application of microbicide candidate.

[5] To test topical microbicides, animals receive a single intravaginal application of the testing compound (formulated or non-formulated) immediately – seconds or minutes – or several hours prior to intravaginal challenge with HSV-2. This approach will identify an effective microbicide that not only protects the animals from viral infection soon after drug application but also retains activity in the genital tract for a considerable period.

[6] In this model, a single dose of the formulated microbicide candidate is applied 30 minutes prior to cervical challenge with a human biotype of *trachomatis* that readily and reproducibly infects 100 percent of challenged animals.

[7] In general, a single dose of a candidate vaginal microbicide is applied to block the establishment of viral infection 15 to 20 minutes prior to the atraumatic administration of virus.

[8] All formulations under development are tested for their effect on the integrity of latex condoms.

[9] Both the NIAID Clinical Research Products Manufacturing Contract and HIV Prevention Trials Network discretionary funds may be used to support packaging and labeling of bulk product for dispensing to study participants.

[10] Through these mechanisms, candidate microbicides that have reached a more mature stage of development, in which the properties of both the active agent and the formulation have been established, enter into clinical trials that ultimately may support a licensure application.

[11] Recently, HPTN investigators have arranged with CONRAD to coordinate Phase I trials of several novel microbicide candidates, with CONRAD conducting Phase I trials among HIV-seronegative low-risk women and HPTN continuing these studies with HIV-infected women.

[12] Periodic meetings of NIAID and FDA staff – sometimes including HPTN investigators – address a variety of issues associated microbicide clinical development strategy. Clinical Trial Agreements (CTAs) and an associated letter of understanding are negotiated with each manufacturer concurrent with the development of trial concepts or early protocol development. NIAID typically holds the IND for agents entering NIAID-funded clinical trials; in those cases where the pharmaceutical company prefers to hold the IND, the CTA specifies which responsibilities (e.g., safety reporting, study monitoring, etc.) the manufacturer delegates to NIAID and/or its grantees or contractors.

[13] This includes the AIDS International Training and Research Program to train developing country scientists by bringing these scientists to U.S. institutions and in exchange supporting in-country activities by U.S. scientists, and the International Bioethics Education and Career Development Award program to develop or expand current curricula in international bioethics related to performing research in low- and middle-income nations.

[14] These contractors assure compliance with human subjects requirements, data integrity, and other standards of Good Clinical Practice. They also offer management and organizational expertise through optional consultation visits to clinical sites seeking advice on how to improve study management and operations.

15 An NIAID-supported grant conducted one of the earliest studies of factors associated with the potential acceptability of various microbicidal formulations among diverse populations of U.S. women at high risk of HIV exposure. More recently, under a program jointly supported by NICHD and NIMH, investigators were invited to submit applications to study the acceptability of new methods – particularly woman-controlled methods such as microbicides – for STI/HIV prevention. An expanded version of the program, on behavioral aspects of microbicides, has been re-issued.

OAR and NIAID convened at a June 2001 workshop on clinical, epidemiological, and behavioral aspects of rectal microbicides, in order to identify key research gaps and to propose clinical research strategies for evaluating safety, plausibility, and efficacy/effectiveness of such products.

A targeted program supported by 16 NIH Institutes, several NIH Centers, ORWH, and CDC supports research on ethical issues in research on human subjects.

16 One particular safety concern, if the microbicide candidate is a marketed therapeutic drug, is the possibility that sub-therapeutic systemic levels of such a candidate may result in selection for and transmission of drug-resistant isolates by users who are unaware of their infected status. Thus, a formulation tailored to optimize activity and minimize irritation potential and systemic absorption becomes a pivotal step for further advancement.

17 Other than HIV and human papilloma virus, sexually transmitted infections can be effectively treated with antibiotics or, as in the case of HSV-2, suppressed.

18 Absence of vaginal protection in clinical trials to evaluate other N-9 containing products argues against clinical evaluations to determine whether N-9 in sexual lubricants enhances the risk of HIV transmission. However, the potential of this detergent to disrupt epithelial surfaces at the time when exposure to HIV is most likely to occur raises an important concern for policy makers and commercial manufacturers of sexual lubricants containing N-9.

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P. 46 — Schematic of the normal cervix, squamocolumnar junction and transformation zone. Coombs R.W. et al. AIDS 2003. 17:455 (2003). Reprinted by permission from publisher, Lippincott Williams & Wilkins

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Cover – Portrait of a man and a woman (right side of globe, between organism photos). Stockphoto: Photodisc/Getty Images

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