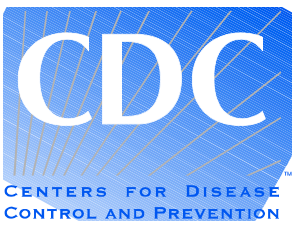
Topical Microbicides for Prevention of Sexual Transmission of HIV

Mission and Research Agenda
FY 2000-2005

22 February 2001



National Center for HIV, STD, and TB Prevention
National Center for Infectious Diseases
National Center for Chronic Disease Prevention and Health Promotion

Table of Contents

Executive Summary

Despite almost 20 years of HIV/AIDS prevention efforts and research, the sexually transmitted HIV epidemic continues to be a major health problem throughout the world and is accelerating in many areas. The identification of a topical microbicide which is effective in significantly decreasing the risk of HIV transmission/acquisition is therefore a high prevention priority both in the US and resource-poor countries, especially when it can be offered in addition to the risk reduction counseling and condom promotion.

While much developmental work and several evaluation studies have been completed in the last few years, the capacity to conduct clinical trials of topical microbicides is currently limited and blocking the development "pipeline". There are now more agents ready for human trials than current research sites can evaluate in the next five years.

Given the multidisciplinary expertise of CDC researchers in clinical trials, nonhuman primate studies, behavioral science, and laboratory studies, our topical microbicide research agenda for the next five years will focus on conducting clinical trials, with strong behavioral and laboratory science underpinnings, to rapidly and ethically assess the safety and efficacy of promising agents for the prevention of sexually-transmitted HIV infection. In addition to a direct effect on HIV transmission, some microbicides could have an added impact by decreasing the transmission/acquisition of other STDs.

The proposed work will extend laboratory and behavioral microbicide studies now underway or recently completed by CDC scientists; expand our domestic and international capacity to field safety and efficacy trials; continue our collaborations with NIH, FDA, academic, private, and community-based organizations involved in topical microbicide development and research; and begin the assessment of implementation strategies should an agent be shown to be effective.

CDC Microbicide Working Group Members

The CDC Microbicide Working Group is comprised of members from the following CDC Divisions:

Division of HIV/AIDS Prevention-Surveillance and Epidemiology, NCHSTP

Division of STD Prevention, NCHSTP

Division of AIDS, STD, TB Laboratory Research, NCHSTP

Division of Reproductive Health, NCCDPHP

Abbreviations Used

CDC	Centers for Disease Control and Prevention
NCHSTP	National Center for HIV, STD, and TB Prevention
NCID	National Center for Infectious Diseases
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
DRH	Division of Reproductive Health
WHFB	Women's Health and Fertility Branch
DHAP-SE	Division of HIV/AIDS Prevention - Surveillance and Epidemiology
DASTLR	Division of AIDS, STD, and TB Laboratory Research
NIH	National Institutes of Health
FDA	Food and Drug Administration
NIAID	National Institute of Allergy and Infectious Diseases
STD	Sexually transmitted diseases
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immune Deficiency Syndrome
DSTDP	Division of Sexually Transmitted Disease Prevention
HIVNET	HIV Network for Prevention Trials
HPTN	HIV Prevention Trials Network
FHI	Family Health International
CONRAD	Contraceptive Research and Development Program
UNAIDS	United Nations AIDS Programme
FY	fiscal year
ESB	Epidemiology and Surveillance Branch
IAB	International Activites Branch
CSW	commercial sex workers
BV	bacterial vaginosis
UTI	urinary tract infection
HARB	HIV/AIDS Research Branch

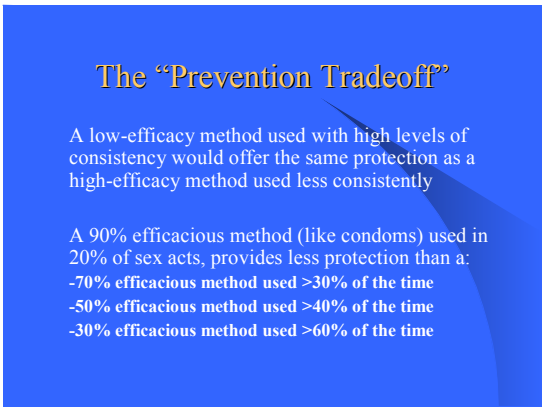
EPIBr	Epidemiology Branch
PCR	polymerase chain reaction
vRNA	viral ribonucleic acid
PBMC	peripheral blood mononuclear cells
PEP	postexposure prophylaxis
MSM	men who have sex with men
HSV	herpes simplex virus
HPV	human papillomavirus
ELISA	enzyme-linked immunosorbent assay
AMP-RT	amplification-based reverse transcriptase assay
CT	Chlamydia Trachomatis
NG	Neisseria gonorrhea
TV	Trichomonas vaginalis
IEL	intraepithelial lymphocytes
LPL	lamina propria lymphocytes
HSREB	Health Services Research and Evaluation Branch
CRADA	Collaborative Research and Development Agreement
IRB	Institutional Review Board
WHO	World Health Organization

I. Rationale for Undertaking Microbicide Research

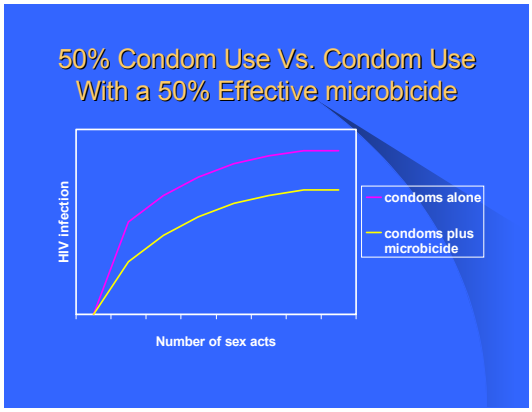
Background

The sexually transmitted HIV epidemic continues to adversely affect people throughout the world and is accelerating in many areas, including the southeast US, southern Africa, Asia, and eastern Europe. This is occurring despite almost 20 years of HIV/AIDS awareness campaigns, behavioral risk-reduction counseling interventions, and aggressive social marketing of male condoms. The development and rapid evaluation of topical microbicides is a critical next step in adding effective new methods to the prevention armamentarium.

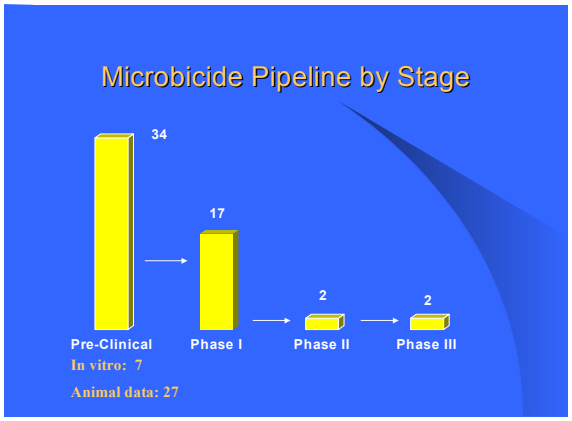
Statistical models presented at the recent Microbicide 2000 conference held in Washington, DC, examined the possible public health benefits of microbicides of varying effectiveness.
These models demonstrated that a high-effectiveness method like the male condom, if used inconsistently or by a minority of the persons at-risk of HIV acquisition, will be of less overall benefit that a less efficacious method (like a microbicide) if it is more acceptable and more commonly used (figure courtesy of Lori Heise).



According to a model developed by Geoff Garnett, striking benefits could come from combining condom use at moderate levels and use of a microbicide with moderate efficacy. In addition to a direct effect on HIV transmission, some microbicides could have an added impact by decreasing the transmission/acquisition of other STDs.



The identification of a topical microbicide which is effective in significantly decreasing the risk of HIV transmission/acquisition is therefore a high prevention priority both in the US and resource-poor countries, especially when it can be offered in addition to the risk reduction counseling and condom promotion.



Because of the critical need for an effective topical microbicide, in recent years many agents have been developed, evaluated, and found in pre-clinical studies to be potentially safe and effective for human use. However, the capacity to conduct clinical trials of these agents is currently limited and blocking the development "pipeline". There are now more agents ready for human trials than current research sites can evaluate in the next five years. Therefore the CDC Microbicide Working Group was formed to review our accomplishments in, and scientific resources for, increasing the evaluation capacity to signficantly improve our chances of finding a safe and effective topical microbicide.

Rationale for increased CDC involvement in microbicide evaluation

As outlined below, CDC staff have conducted laboratory, clinical, and behavioral studies related to microbicides and are participating in the planning and implementation of clinical trials by several collaborating agencies. We have been involved as consultants for several years, working with agencies and programs such as NIH, HIVNET/HPTN, FHI, the Population Council, CONRAD, UNAIDS, and the Alliance for Microbicide Development, as their microbicide research agendas have developed.

The CDC research agenda set forward in this document by the Microbicide Working group makes use of our: 1) experience with, and responsibility for, HIV prevention research and programs; 2) ability to rapidly mount and execute domestic and international studies, including clinical trials; and 3) availability of scientists with clinical, epidemiological, laboratory, statistical, behavioral, and ethics expertise, who are already experienced in the types of collaboration necessary for this complex work.

Microbicide research has been funded at relatively low levels in recent years, <1% of the federal HIV/AIDS research budget. However, the Microbicide Development Act of 2000 now pending in Congress will provide additional, targeted funding to NIH and CDC for microbicide research. The request for CDC is 7 million in FY2001, 10 million in FY2002, and 15 million in FY2003. This document describes a coordinated, long-term agenda for both the use of existing funds which may come available within CDC and additional research for which new funding and personnel will be sought.

This document refers to the study of agents intended to reduce HIV transmission, some of which may also be active against STDs. If microbicide trials for HIV prevention demonstrate efficacy in STD prevention also, they may have a larger public health benefit than those efficacious against HIV only. The primary focus of the work proposed will be on prevention of heterosexual penile-vaginal HIV transmission because it is the primary mode of transmission worldwide and a fast-increasing route of transmission in the US. However, because MSM transmission is still the

primary route of transmission in the US, and because any topical microbicide found effective in reducing penile-vaginal transmission may quickly be adopted for use by women and men engaging in anal sex, work will also be done to develop and then apply laboratory and other methods necessary to examine the safety and acceptability of candidate agents when applied to rectal mucosa

II. Mission Statement and Goals

The mission of the CDC Microbicide Working Group is to contribute to the rapid evaluation of safe and effective microbicides for the prevention of sexual transmission of HIV.

This mission will be achieved by achieving the following goals:

- Conducting intramural and extramural laboratory research in preparation for, and support of, clinical microbicide trials.

- Conducting intramural and extramural behavioral research in preparation for, and support of, clinical microbicide trials.

- Developing and characterizing domestic populations and international cohorts appropriate for Phase I, II, and III clinical trials of candidate topical microbicides for the prevention of HIV infection.

- Efficiently conducting Phase I and II clinical trials to assess the safety and acceptability of candidate microbicides.

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- Efficiently conducting Phase III clinical trials to assess the efficacy of candidate microbicides.

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- Providing technical assistance to, and consultation with, a wide variety of domestic and international entities involved in developing and evaluating topical microbicides; including health agencies, extramural researchers, industry, activists, and non-profit organizations.

- Developing and evaluating the diffusion and effects of implementation strategies for use of effective topical microbicides for HIV prevention.

III. Past and Current Research and Activities

The first meeting of the CDC Microbicide Working Group was devoted to review of past and current work done at CDC in this area. The recent studies and activities cited below have specific utility to planned microbicide trials.

A: Clinical Studies and Trials

A1. A Prospective, Observational Cohort Study to Determine the Incidence of HIV-1 Infection in Women Postpartum and Women Attending Family Planning Clinics.- NCHSTP/DSTDP/ESB, NCHSTP/DHAP-SE/IAB, Thailand Ministry of Public Health

CDC Project Officer(s): Peter Kilmarx, MD.

Abstract: From July 1998 to January 2000, this study was conducted evaluate the feasibility of vaginal microbicide studies in this population. Women were enrolled from 11 family planning clinics and one postpartum ward in upper northern Thailand into a prospective, observational study. At enrollment and at 6- and 12-month follow-up visits, consenting women were interviewed and tested for HIV antibodies. To reduce HIV transmission risk, at each visit male condoms were provided, condom use was demonstrated, and HIV testing for the husband was recommended.

Findings:

- The median age of the 804 participants was 27 years, 98% were currently married, and 3.1% were HIV seropositive.
- Of all infections, 76% were in the 665 women (83%) who had never had a casual sex partner.
- From family planning clinics, 655 HIV-seronegative women (54% of those recruited) were enrolled; 96% returned for 12-month follow-up; and 1 women seroconverted (0.19 per 100 person-years).
- From the postpartum ward, 124 seronegative women (11% of those recruited) were enrolled; 78% returned for 12-month follow-up; and none of the women seroconverted.

- These data suggest that this would be a good population for microbicide safety and acceptability trials. HIV incidence was low; thus, HIV-prevention efficacy trials do not seem feasible in this population.

A2. COMMUNITY CONSULTATION IN PREPARATION FOR CLINICAL TRIALS IN NORTHERN THAILAND: THE CHIANG RAI MICROBICIDE RESEARCH COMMUNITY ADVISORY GROUP

- NCHSTP/DSTDP/ESB, NCHSTP/DHAP-SE/IAB, Thailand Ministry of Public Health, Population Council

CDC Project Officer(s): Peter Kilmarx, MD.

Abstract: This activity was undertaken to form a community advisory group to enhance research quality and responsiveness to community needs. We formed the "Chiang Rai Microbicide Research Community Advisory Group" during protocol development for vaginal microbicide clinical trials. The 12 members (10 of whom are women) are local community leaders and persons drawn from community-based organizations, local health centers, commercial sex establishments, and the research group. During the six meetings in the first year, the group learned about their expected role, and attained a good understanding of vaginal microbicide research and development, and clinical trial concepts such as randomization, blinding, and use of a placebo. The study protocol, consent forms, and patient educational materials were reviewed in detail and, as a result of the consultation process, we made numerous modifications to these.

Findings:

- Establishment of a community advisory group is especially useful in developing study procedures, consent forms, and patient education materials.

- The research team also gained valuable experience in communicating complex ideas to potential participants.

- Other research groups in the region have been very interested in emulating this activity.

A3. Study of Safety and Acceptability of Vaginal Gel Formulation PC-503 for Intravaginal Use as a Possible Microbicide - NCHSTP/DSTDP/ESB, NCHSTP/DHAP-SE/IAB, Thailand Ministry of Public Health, Population Council

CDC Project Officer(s): Peter Kilmarx, MD.

Abstract: This study, conducted from September 1997 to June 1998, sought to determine the safety and acceptability of vaginal gel formulation PC-503 among low-risk, abstinent women. The active ingredient was 2% pharmaceutical grade *lambda*-carrageenan, a sulfated polymer. Thirty-five women in Thailand (and four other international sites) applied 5 ml of the PC-503 gel vaginally once a day for seven days while abstaining from sexual intercourse. Visual vaginal exams were performed on Days 1, 4, and 8. STD testing and vaginal pool gram stain preparations were done on Days 1 and 8. Participants were asked about product acceptability.

Findings:

- Thirty-four of the 35 women enrolled completed seven days use.
- Following product use, five reported mild symptoms including "bladder fullness," genital warmth" or discomfort, and lower abdominal pain, and one had moderate pale yellow cervical discharge.
- Most of the women found PC-503 to be pleasant or neutral in feel and smell and considered extra lubrication to be an advantage; however, one third found it to be messy.
- As a result of this study the product was reformulated to have a higher concentration and a smaller volume before going on to further evaluations.

A4. A Randomized, Placebo-Controlled, Double-Blind Trial to Assess Expanded Safety, Acceptability, and Preliminary Effectiveness of PC-515 (Lambda Carrageenan) for Vaginal Use as a Possible Microbicide- NCHSTP/DSTDP/ESB, NCHSTP/DHAP-SE/IAB, NCID/DASTLR, Thailand Ministry of Public Health, Population Council

CDC Project Officer(s): Peter Kilmarx, MD.

Abstract: The primary aims of this study (January 2000 - December 2001) are to assess the toxicity of PC-515 gel when applied vaginally several times per week for twelve months and to examine several dimensions of the acceptability of the study and placebo (methyl cellulose gel) products. It will also begin to assess the effectiveness of PC-515 in prevention of male-to-female transmission of HIV, *C. trachomatis, N. gonorrhea, T.*

vaginalis, T. pallidum, and HSV-2 as well as its impact on bacterial vaginosis, vaginal candidiasis, and cervical cytology. This randomized, placebo-controlled, double-blind trial will enroll 165 women for one year from family planning clinics, including 25 women for a nested preliminary safety study of the first 25 woman-months of gel use. If PC-515 appears safe and acceptable in this study, the product sponsor can proceed to phase III efficacy testing.

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Progress to date: The preliminary safety study (25 women followed for one month) is completed. We are awaiting approval from our data and safety monitoring board to proceed to full study enrollment.

Preliminary Findings:

- Screening, enrollment, and follow-up went well.
- No one has discontinued product use due to adverse events.

A5. A RANDOMIZED DOUBLE-BLIND PROTOCOL COMPARING COL-1492 WITH PLACEBO IN THE PREVENTION OF MALE-TO-FEMALE TRANSMISSION OF HIV AND STDS. A MULTI-CENTRE PHASE III STUDY AMONG WOMEN AT HIGH RISK OF HIV INFECTION -

NCHSTP/DHAP-SE/IAB, Côte d'Ivoire Ministry of Health, UNAIDS.

CDC Project Officer(s): Stefan Wiktor, MD

Abstract: From 1996 through May 2000, this study was conducted in Abidjan (and 3 other international sites) to assess the safety of long term administration of COL-1492 (52 mg of nonoxynol-9 in a bioadhesive carrier), to assess the efficacy of COL-1492 in the prevention of STDs and HIV transmission, and to assess the acceptability of COL-1492 among study participants (female commercial sex-workers (CSWs) participating in a programme to promote100% condom use). 991 seronegative women in four sites worldwide applied 1.5 ml of the COL-1492 gel vaginally before each act of sexual intercourse Women were followed for 24 months with periodic visual vaginal exams, HIV serology, STD testing, vaginal pool gram stain preparations, cervicovaginal lavage to assess mucosal immunity, a cervical cytology sample, assessments of compliance with condom and study medication use, and collection of coital logs. In addition, 150 HIV seropositive women were enrolled and followed in the same manner as seronegative women to assess the effect of COL-1492 and STDs on cervicovaginal HIV shedding.

Findings:

- In June 2000, the Data Safety and Monitoring Board reported that 100 women had become infected, more in the COL-1492 group than in the placebo group.
- Completion of this study allowed determination that this low-dose N9 product is not effective in preventing HIV infection in CSWs and may in fact be harmful.

B: Non-human Primate Studies

B1. Efficacy of Post-exposure Prophylaxis (PEP) after Intravaginal Exposure of Pig-tailed Macaques with a Human-derived Retrovirus (HIV-2) - NCID/DASTLR/HARB and NCHSTP/DHAP-SE/EpiBr

CDC Project Officer(s): Ron Otten, PhD and Dawn Smith, MD

Abstract: In 1998 and 1999, this study was conducted to: 1) Determine in vivo infectious doses required to establish systemic HIV-2 infection of macaques by mucosal (intravaginal) route, 2) evaluate PEP regimens with a potent antiretroviral agent (PMPA) as an optimal intervention strategy toward preventing HIV-2 infection following mucosal exposures that mimic those of human sexual contacts, and 3) investigate the potential utility of a prototype PCR- based vRNA quantitative assay for evaluating plasma and cervicovaginal virus loads in HIV-2 exposed macaques. Sixteen naive experimental female animals were exposed by atraumatic inoculation of cell-free virus into the vaginal pouch . PMPA, a nucleotide analog inhibitor, was given by subcutaneous injection for 28 days starting 12, 36, or 72 hours after viral inoculation. Blood and tissue specimens were collected longitudinally to evaluate plasma and cervicovaginal virus levels, presence of provirus in PBMC, and serologic responses. Lymph node biopsies were taken for detection of virus dissemination.

Findings:

- Macaques in the 12 and 36 hour post exposure treated groups were protected from systemic infection and remained seronegative through 24 weeks post infection.
- One confirmed seroconversion in the 72-hour group was observed at week 16 post infection indicating delayed, systemic infection and PEP failure
- Findings indicate that early intervention with a potent antiretroviral regimen may be successful in preventing infection via vaginal exposure to a human derived retrovirus

- This transmission interruption model has been adapted for rectal HIV-exposures and will be used next for microbicide studies.

B2. Efficacy of Pre- and Post-intravaginal Microbicide Application Toward Preventing Retroviral(HIV-2) Infection in a Macaque Mucosal Exposure Model - NCID/DASTLR/HARB and NCHSTP/DHAP-SE/EpiBr

CDC Project Officer(s): Ron Otten, PhD and Dawn Smith, MD

Abstract: Using an in vivo mucosal exposure model, this study, to be begin in September 2000, will investigate the in vivo efficacy of, and determine optimal timing of administration of, selected microbicides in preventing chronic, systemic infection in pig-tailed macaques exposed vaginally or rectally to a human-derived retrovirus (HIV-2). The study will also examine whether localized virus replication occurs at the exposure site prior to systemic spread and possibly in the absence of a disseminating infection. Use of 28 pigtail macaques will permit evaluation of 2 microbicides, each at 3 different treatment time points. After virus exposure, longitudinal blood and tissue specimens will be collect for 6 months and used to determine plasma and cervicovaginal virus levels, provirus detection in PBMC, virus isolations, and serologic responses. Tissue biopsies will be analyzed for detection of localized virus replication at mucosal exposure site. This data may ultimately provide part of a solid basis for establishing guidelines for microbicide use in the prevention of human sexual HIV transmission

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C: Behavioral Studies

C1. Acceptability of Barrier Contraceptives to Women in Zimbabwe - DHAP-SE/EpiBr, Harare, Zimbabwe

CDC Project Officer(s): Jan Moore, PhD

Abstract: This study (conducted October 1996 to September 2000) is designed to: 1) determine the acceptability of various HIV/STD prevention methods (i.e., male condom, female condom, spermicide) and, 2) evaluate a model for presenting women with multiple HIV/STD prevention options Approximately 500 women were recruited from family planning and primary health clinics in Harare to participate in a two-session intervention shown in previous research to increase male condom use. Male condoms were supplied to participants and data on patterns and barriers to use were collected at three months. Women

who were unable to use male condoms with some consistency following the intervention (i.e., male condom use <75% of the time for vaginal or anal sex) were eligible for the second phase of the study in which alternative HIV/STD prevention methods (female condoms and vaginal contraceptive gel) were offered. Women in Phase II received the three HIV prevention options presented in a hierarchy from most to least efficacious. Male condoms, female condoms, and vaginal contraceptive gel were dispersed to women for use during the following three months. Data on patterns of use for all three methods were collected at the end of three months. This study seeks to develop an HIV/STD prevention plan that ensures that as many women as possible use male condoms as often as possible, but use alternative methods, even though they may be less effective, when male condoms can not or are not used. If successful, this type of prevention plan could result in an increased number of protected sexual acts among women at risk for heterosexual transmission of HIV.

Progress to date:

- Approximately 37% of women enrolled in the study were found to be HIV infected and discontinued from the intervention.

- Of the remaining women, almost two-thirds used male condoms consistently by the three month follow-up visit

- All women eligible for Phase II of the study (one-third of women completing Phase I) completed the intervention and follow-up assessment by June 2000. Conclusion of this study predated the release of the UNAIDS Col 1492 study results documenting increased HIV transmission among commercial sex workers using a nonoxynol 9 containing product. Procedures have been instituted to inform the study participants about the UNDAIDS study results and to offer them repeat HIV testing.

C2. ACCEPTABILITY OF BARRIER CONTRACEPTIVES TO WOMEN IN THE US -

NCHSTP/DHAP-SE/EpiBr, Dade and Broward Counties, FL, Los Angeles, CA

In the US (Los Angeles and Miami) women are being recruited from health clinics and enrolled into microbicide acceptability studies using Advantage S. In Phase 1, male condom use is maximized and at the end of Phase 1, those with ≤75% condom use are enrolled into the Phase 2 study; a multiple option intervention during which acceptability of female condom and spermicidal products are evaluated. Screening of large numbers of women (3000 in the US) for Phase I was necessary to enroll 2-300 women for Phase II.

CDC Project Officer(s): Janet R. Saul, PhD

Abstract: Beginning in 1997 and concluding in 2001, this study is designed to 1) determine

the acceptability of various HIV/STD prevention methods (i.e., male condom, female condom, spermicide) and, 2) evaluate a model for presenting women with multiple HIV/STD prevention options Women first participate in a brief intervention shown in previous research to increase male condom use. Male condoms are supplied to participants and data on patterns and barriers to use are collected at three months. Women who are unable to use male condoms with some consistency following the intervention in the first phase of the study (i.e., male condom use <75% of the time for vaginal or anal sex) are eligible for the second phase of the study in which alternative HIV/STD prevention methods (female condoms and vaginal contraceptive gel) are offered. In Phase II, one-half of the eligible women are randomly assigned to receive the "multiple option" intervention with options presented in a hierarchy. The other half of the women are assigned to the control, "single option" condition, in which they continue to receive a male condom intervention.

Offering women multiple HIV/STD prevention options is not without problems. If women who are using (or would consider using) the male condom, substitute methods that may be easier to use, but are less effective, then offering multiple options could inadvertently reduce HIV/STD protection for women. The current study seeks to develop an HIV/STD prevention plan that ensures that as many women as possible use male condoms as often as possible, but use alternative methods, even though they may be less effective, when male condoms can not or are not used. If successful, this type of prevention plan could result in an increased number of protected sexual acts among women at risk for heterosexual transmission of HIV.

Progress to date: 33 women have completed Phase I of the study, and 184 additional women are pending their final visit of Phase I. Of the 33 who completed Phase I, 20 (61%) were eligible for Phase II. All 20 women who were eligible for Phase II enrolled. As a result of preliminary data released from the UNAIDS Col 1492 trial, that reported a higher HIV transmission rate among commercial sex workers using Advantage S than those using placebo, Phase II was temporarily discontinued on 6/19/2000. Study investigators contacted all women who had received Advantage S and retrieved any remaining product. The trial was modified and resumed in August 2000 without use of any microbicidal agents. All references to spermicide as an HIV prevention method were removed from materials provided to participants and instead, women will be asked about their interest in, and willingness to use, a microbicide if one becomes available.

C3. A Study of Male Peripartum Sexual Behavior Norms, Related Changes in Commercial Sex Worker Patronage, and Perceptions of Risk for HIV among Antenatal Care Clients in Northern Thailand - NCHSTP/DSTDP/ESB, NCHSTP/DHAP-SE/IAB, Thailand Ministry of Public Health, Population Council

CDC Project Officer(s): Peter Kilmarx, MD.

Abstract: This study, conducted from June 1996-December 1998, investigated women's perception of risk for acquiring HIV, their husband's HIV risk behavior (particularly in the peripartum period), and women's and men's attitudes toward the clinical evaluation and use of vaginal microbicidal products to limit sexual HIV transmission between regular partners. We conducted eight focus group discussions with women and eight with men as well as in-depth interviews with 40 women and 40 men. In addition, we conducted structured questionnaire surveys among 370 women (276 from an antenatal clinic and 94 from a family planning clinic).

Findings:

- Although the women participants believed that it was common for men to visit sex workers, and that this could be linked to their own risk of HIV infection, they generally did not perceived themselves to be at risk of HIV.

- Women and men both described a peripartum sexual abstinence norm averaging 6-9 months and agreed that a significant proportion of men would be likely to seek alternative sexual partners during the peripartum period, thereby putting their wives at risk of HIV infection.

- Women and men both reported low levels of marital condom use and expressed considerable interest in the potential for vaginal microbicides and in trial participation.

- We were able to demonstrate that a short (30-45 minute) educational session was a successful means of informing a population of women previously unacquainted with the concept of microbicides or clinical trial design in this setting in Northern Thailand.

C4. MICROBICIDE ACCEPTABILITY AMONG WOMEN AT RISK FOR STDS -

NCCDPHP/DRH/WHFB, CDC Office of Women's Health, University of Alabama, Birmingham

CDC Project Officer(s): Sam Posner, PhD

Abstract: This study, conducted in 1998-1999 in Birmingham, determined the acceptability of a microbicide for women who were at risk for HIV/STD or unintended pregnancy if one were to become available. We also examined product characteristics that might be important factors in acceptability of the product. A total of 415 women were enrolled in the study and completed an interviewer administered survey on microbicide acceptability.

Findings:

- the overwhelming majority of women reported that they would use the hypothetical product.

- there appeared to be no respondent preference for product characteristics in determining acceptability.

- preliminary findings of this study and a previous study of spermicide acceptability suggest that research on hypothetical products has little relevance to actual product acceptability.

C5. SELLING SAFER SEX: MEANING, MOTIVES AND MESSAGE COMPLEXITY - NCHSTP/DHAP-SE, West Hollywood, CA

CDC Project officer(s): Gordon Mansergh, PhD and Gary Marks, PhD

Abstract: Development of an effective rectal microbicide holds promise for HIV prevention. From 1996 to 1998, this study examined men's personal efficacy standards (i.e., preferences about product efficacy) for a future rectal microbicide and intentions to use it during anal intercourse. Three hundred eighty-five men who have sex with men (MSM), sampled in West Hollywood, California completed a behavioral questionnaire, read a detailed description of a potential rectal microbicide gel and expressed their preferences about product efficacy and intended use. The sample was 24% African American, 29% Hispanic, and 47% white.

Findings:

- On average, participants wanted a microbicide gel to be 84% effective in preventing HIV infection before they would use it as the only means of protection during anal intercourse; 53% of the men wanted the gel to be at least 95% effective.

- In multivariate analyses, intention to use the gel by itself was associated with higher efficacy standards for the microbicide, negative attitudes about using condoms, and a history of unprotected anal intercourse.

- 37% of the men who always used a condom during anal sex in the past year said they would be more likely to use a microbicide gel than a condom in the future; however, 85% of this subgroup wanted the gel to offer protection comparable to a condom before they would use it alone.

- These findings indicate that even a moderately effective rectal microbicide may have a sizable public health benefit because it provides an alternative for MSM who dislike condoms.

D: Laboratory Studies

D1. In Vitro Testing of Candidate Vaginal Microbicides for Toxicity and Antiviral Activity Against Human Immunodeficiency Virus Type - NCID/DASTLR/HARB

CDC Project Officer(s): Clyde Hart, Ph.D.

Abstract: Beginning June 2000, our laboratory will test 3 candidate vaginal microbicides for cellular toxicity and induction of proinflammatory cytokine production in cell cultures of human peripheral blood mononuclear cells (PBMCs) and a cell line derived from human cervical cells (ME180). Cellular toxicity is being determined by cell viability and replication kinetics over a 7-day cycle. Non-toxic concentrations of microbicides are tested for anti-HIV-1 activity in cell cultures of CD4+ lymphocytes and monocytes. In addition, we will assay for increased production of proinflammatory cytokines in cell cultures containing non-toxic concentrations of microbicides. PBMCs will be assayed for HIV-1 infection after 7 days in culture using an HIV-1 antigen detection system. To assess antiviral activity in an environment that is more representative of that found during sexual intercourse, further in vitro testing of the microbicides effectiveness against HIV-1 will be performed in the presence of human semen and cervicovaginal secretions. The adoption of a more thorough and realistic in vitro testing paradigm of vaginal microbicides will provide a more cogent background for determining which products should be considered for human testing.

Preliminary findings

- higher concentrations of proinflammatory cytokines in genital secretions have been associated with higher levels of vaginal virus in HIV-1-infected women. Therefore, it will be important to know if non-toxic levels of the microbicides increase production of these cytokines. .

D2. Quantifying Cervicovaginal Viral and Immunologic Factors - NCID/DASTLR/HARB and NCHSTP/DHAP-SE/EpiBr

CDC Project Officer(s): Clyde Hart, Ph.D and Julie Villanueva, Ph.D.

Abstract: The assays listed below were assessed and standardized to give an accurate assessment of the presence of HIV in the female genital tract. Not only can we quantify the

amount of virus present in genital secretions, but also we can determine whether this virus can replicate and/or infect other cells. Because different microbicides have different mechanisms of action, it is crucial to determine their specific effects on the virus. These assays are designed primarily to detect and quantify HIV-1. However, protocols can easily be modified to detect other viruses such as HSV and HPV.

Important assays ready for use in microbicide clinical trials include:

- Quantitative, competitive PCR technique to quantify HIV-1 loads from vaginal and cervical secretions
- Ultra-sensitive ELISA-based assays to quantify cytokines, which have been shown to enhance or inhibit virus production, in vaginal and cervical secretions.
- AMP-RT assay to quantify replication-competent HIV-1 in female genital secretions.
- Overnight cell culture infectivity assay to assess the ability of virus isolated from genital tract secretions to infect other cells.
- In situ hybridization coupled with immunocytochemistry on cell slide preparations from genital secretions to determine exactly which types of cells are associated with virus.

D3. ASSESSMENT OF EFFECT OF MICROBICIDES ON COBAS AMPLICOR and GEN-PROBE CHLAMYDIA TRACHOMATIS AND NEISSERIA GONORRHEA, AND INPOUCHTV TRICHOMONAS VAGINALIS TESTS - NCHSTP/DSTDP/ESB, NCHSTP/DHAP-SE/IAB, NCID/DASTLR, Thailand Ministry of Public Health, Population Council

Project Officer(s): Nancy Young, MS, MT(ACSP)

Abstract: Conducted from June 1999 to December 2001, this study will assess whether sexually transmitted disease test results that use genital specimens are compromised by contamination with vaginal microbicides. Different cervical-simulated dilutions of control organisms Chlamydia trachomatis (CT) and Neisseria gonorrhea (NG) plus the microbicide, are tested with the Amplicor CT/NG PCR and Gen-Probe nucleic acid hybridization test kits. A vaginal-simulated dilution of ~$2.4x10^5$ Trichomonas vaginalis (TV) organisms plus the microbicide are added to the InPouch TV medium to observe for growth inhibition.

Progress to date: Completed *in vitro* assessment of PC-515 (carrageenan) and methyl-cellulose placebo gels. Manufacturers of other candidate microbicides are also sending samples for this evaluation.

Findings:

- No inhibition with placebo for any test at any dilution was observed.
- In the presence of PC-515, varying degrees of inhibition were exhibited for both the Amplicor and Gen-Probe tests when used according to manufacturers' standard instructions.
- A modified collection and processing procedure in which a chlamydia transport medium and PBS wash were used eliminated all inhibition from the Amplicor test, but not from the Gen-Probe test.
- With PC-515, the InPouch TV medium demonstrated a mean of 6% growth inhibition at 24 hours, but >70% growth inhibition at 48 hours.
- The impact of microbicide and placebo products on laboratory tests for STDs must be known to interpret microbicide trial results correctly. Some test results may be inaccurate and some test procedures may require modification.

D4. Evaluation of Microbicides for Mucosal HIV/STD Transmission using Cervical Tissue Explants - NCID/DASTLR/HARB, NCHSTP/DHAP-SE/EpiBr, Emory University

CDC Project Officer(s): Charlene S. Dezzutti, PhD and James E. Cummins, Jr., PhD

Abstract: Beginning in September 2000, this study will use cervical tissues collected from women undergoing hysterectomy to isolate intraepithilial (IEL) and lamina propria lymphocytes (LPL) and intact cervical tissue for use in evaluating microbicides. Studies will examine 1) maintenance of the epithelial layer, 2) reduction of HIV-1 replication from IEL and LPL, and 3) prevention of STD (*Treponema pallidum*, *Neisseria gonorrhea*, or *Trichomonas vaginalis*) activation of immune cells or degradation of the epithelial barrier. The effectiveness of pre- or post-treatment with the microbicide will be evaluated by measuring HIV-1 replication. Our model system would allow us to better evaluate the early phases of topical microbicides by approximating an in vivo human environment.

Preliminary findings

- HIV-1 does not infect cervical or prostate epithelial cells and therefore, these cells are not directly responsible for transmission.

- The integrity of the epithelial barrier is important for preventing HIV-1 passage to the underlying stroma and immune cells.

- *T. pallidum*, but not *N. gonorrhea*, can induce HIV-1 replication from infected lymphocytes

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E: Representation

E1. UNAIDS CONSULTATION

Dr. Katy Irwin (NCHSTP/DSTD/HSREB), Dr. Lynn Paxton (NCHSTP/DHAP-SE/EpiBr), and Dr. Ann Duerr (NCCDPHP/DRH/WHFB) have represented CDC on the International Microbicide Working Group convened by UNAIDS. This interaction allows CDC to stay abreast of currently funded and planned microbicide clinical trials in order to develop a CDC research agenda complementary to work by others.

E2. HIV PREVENTION TRIALS NETWORK (HPTN) CONSULTATION

Dr. Lynn Paxton (NCHSTP/DHAP-SE/EpiBr) and Dr. Jan Moore (NCHSTP/DHAP-SE/EpiBr) sit on the HPTN microbicide Science Working Group, and Dr. Paxton on the antiretroviral therapy Science Working Group. Dr. Helene Gayle, Director of the National Center for HIV, STD, and TB Prevention at CDC, sits on their Executive Committee. This interaction allows CDC to stay abreast of NIH funded microbicide clinical trials and so will make possible the development and implementation of a CDC research agenda complementary to NIH trials.

IV. Planned Research Activities

After review of the field and the work already undertaken at CDC, the Microbicide Working Group has identified the following strategies and research plans. CDC will:

STRATEGIES:

- Identify study designs and methods, research sites, and both intramural and extramural collaborations appropriate for rapid, valid, and ethical assessment of the safety and efficacy of candidate microbicides (see Table 1).
- Conduct Phase I/II clinical trials for safety and dosing in cervicovaginal, penile/urethral, and rectal application; and for effect on cervicovaginal viral shedding and inactivation in HIV-infected women.
- Conduct Phase IIB/III efficacy trials in high-risk heterosexual cohorts. Products found safe and effective in these trials will then be tested for efficacy when applied rectally.
- Maximize the complementarity of CDC work with work funded by NIH, UNAIDS, and other extramural collaborators.
- Until additional external funds designated for microbicide studies are available, use existing CDC core resources for preparatory work for phase III efficacy trials, including collaboration with international field stations and urban research centers, add-ons to existing studies, and reprioritized funding from center, division, and branch funds.

While there are more than 60 candidate agents in various stages of preclinical testing or early clinical trials, initially we will focus on completing human safety and efficacy trials of one or more microbicides which are now in early clinical trials, listed in Table 1.

Table 1
Microbicide candidates with at least one phase I clinical trial*
(those with at least one phase 1 trial planned or underway as of January 30, 2001

Agent	Mechanism of action	STD activity	Contra-ceptive activity	Phase I safety		Phase II safety/dosing		Phase III Efficacy
				HIV-♀	HIV+♀	HIV-♀	HIV+♀	HIV-♀
PC 515/ Carraguard λ carageenan	**binding inhibitor**	**HSV-2 GC,CT HPV**	**?**	**√**	**P**	**F**		**P**
Pro2000	**binding inhibitor**	**HSV-2 CT, GC**	**hi-dose only**	**√**	**F**	**F**	**P**	**P**
PMPA gel	**virucidal**		**no**	**P**	**P**		**P**	
Dextrin sulfate	**binding inhibitor**		**?**	**√**		**F**		**P**
BufferGel	**maintain lo vaginal pH**	**HSV-2 CT**	**yes**	**√**		**F**		**P**
Invisible Condom	**chemical barrier**	**HSV-2**	**no**	**F**				
Savvy/C31G	**surfactant**	**GC, CT HSV**	**yes**	**√**		**F**		

√ = at least one trial completed **F** = at least one trial in the field
P = at least one trial planned and funded, but not yet started

* data from the February 2001 microbicide product database provided by the Alliance for Microbicide Development

Given these strategies and given the multidisciplinary expertise of CDC researchers in clinical trials, nonhuman primate studies, behavioral science, and laboratory studies, our topical microbicide research agenda for the next five years will focus on conducting clinical trials, with strong behavioral and laboratory science underpinnings, to rapidly and ethically assess the safety and efficacy of promising agents for the prevention of sexually-transmitted HIV infection.

ACTIVITIES:

A. Preparatory Work for Clinical Trials

Year 1

CDC will form a small working group to review in-vitro, animal study, and safety criteria for evaluating microbicides developed by other groups (e.g, HPTN) and define the criteria which will be used to select agents for early clinical trials. By these criteria, 2-3 microbicides will be selected for early CDC-funded clinical trials.

At the same time, internal and external consultations with epidemiologists, statisticians, and ethicists will be held to decide on ethical and highly effective trial designs for use in the initial CDC -sponsored clinical trials and to select the most appropriate population groups (e.g., general population, discordant couples, commercial sex workers) to recruit into the various trials.

Discussion with project officers for domestically funded research projects and with the senior research staff at the CDC field stations in Thailand, Cote d'Ivoire, Kenya, Uganda, and Botswana will be held to establish their interest in, capacity for, and suitability of their accessible populations for, phase I and II trials to be rapidly initiated.

B. Laboratory and Nonhuman Primate Research In Support of Clinical Trials

Years 1-5

Laboratory scientists working on microbicide-related research will establish relationships (including CRADAs) with biotech/pharmaceutical companies producing microbicides selected for initial clinical trials and others under consideration.

Laboratory scientists, in collaboration with epidemiologists designing the trials, will address key scientific questions necessary to conduct effective safety and efficacy studies for macaque and human vaginal, penile, and

ACTIVITIES: (cont.)

rectal applications. This may include basic science research about transmission events, immunologic or virologic factors related to transmission, assay development or adaptation, or other studies. These studies will be ongoing as new products are evaluated and as new questions arise.

YEARS 2-5

As sites for larger phase II and phase three trials are being developed, laboratory researchers will play a critical role in standardizing laboratory technologies and transferring the ability to perform them to trial sites. This will include not only training activities but all quality control of key laboratory assays at distant microbicide study sites.

C. BEHAVIORAL RESEARCH IN SUPPORT OF CLINICAL TRIALS

YEAR 1

Behavioral scientists will need to develop, test, and standardize microbicide acceptability measures and instruments as well as culturally appropriate self-report behavioral measures (e.g., sexual behavior, product use) for initial small phase I and II trials.

Behavioral scientists and epidemiologists will work together to design and implement community preparedness activities for clinical microbicide trials, building on our experience with vaccine trial preparedness domestically and internationally. They will also work together to design and conduct studies to assess issues in informed consent, particularly for phase II and III trial participants.

YEARS 2-5

Behavioral researchers will play the key role in developing and testing methods for presenting multiple HIV prevention options of differing efficacy, assessing the level of understanding of phase II and III trial participants of these messages, and evaluating the interaction of relationship factors and product use.

In addition, the work done on behavioral measures in year 1 will need to be expanded and revisited as additional trials are planned and implemented.

ACTIVITIES: (cont.)

D. CLINICAL TRIALS

PHASE I/II SAFETY TRIALS-YEAR 1

Following discussions with FDA staff, study protocols to evaluate safety and dosing will be written and submitted to the involved IRBs. Ongoing communication with trialists at NIH and other funded microbicide research sites will assist this process.

At least one domestic and one international research site will be selected for the conduct of safety trials. Site development will be completed, including work with laboratory, behavioral, data management, and site staff development issues.

One or more safety trials will be done with topical microbicides (selected by the agreed upon criteria) in collaboration with appropriate and interested CDC-funded domestic and international research sites. Whenever possible, these will be done as add-on studies to compatible protocols.

YEARS 2-5

As additional microbicides are developed which meet the CDC selection criteria, additional phase I and II trials will be conducted.

PHASE IIB/III EFFICACY TRIALS YEARS 2-3

Evaluations of sites appropriate for microbicide efficacy trials will be conducted, including the documentation of HIV incidence rates and condom use rates in potential study populations.

A competitive announcement will be written, objective review of applications conducted, and at least one site for efficacy trials selected for funding.

PHASE IIB/III EFFICACY TRIALS YEARS 3-5

In collaboration with site investigators, site preparation will be done and study protocols finalized. This will include providing community education and recruiting community involvement.

At least one phase III efficacy trial of a vaginal microbicide will be conducted. If it proves possible to do these trials at existing CDC field stations, they could be begun a year earlier (in year 2) since considerable infrastructure will already be present and community relationships well

ACTIVITIES:

(cont.) developed..

CLINICAL TRIALS - TIME DEPENDENT TASKS

When a vaginal microbicide is proven effective in reducing HIV transmission, we will assess its acceptability and efficacy for rectal use. This will involve laboratory and behavioral preparatory studies in addition to clinical trials.

E. TECHNICAL ASSISTANCE

Coordination and collaboration will continue with NIH (HPTN), UNAIDS, the Population Council, UNAIDS and others to select agents and trial designs, share experience, and avoid uninformative duplication of effort.

Coordination and collaboration with activist and community groups involved in microbicide research issues (e.g., Alliance for Microbicide Development) will continue and be expanded to ensure community input into trial designs and to facilitate the translation of research findings to the populations interested in use of effective microbicides.

F. IMPLEMENTATION AND POLICY

Should a vaginal microbicide be shown to be effective in reducing HIV transmission, research on implementation strategies will be designed and conducted both internationally and domestically. These will include modeling studies to assess population effects and cost- benefit of microbicide use under varying conditions.

SUMMARY

The CDC microbicide working group will capitalize on its interdisciplinary expertise in clinical trials, laboratory sciences, behavior sciences, and epidemiologic research, and will work closely with our public health partners (FDA, NIH,USAID, UNAIDS, WHO), with organizations outside the government, and with foundations, to support the implementation of this research agenda as a means to contribute to the global effort to identify a safe and effective vaginal microbicide.