

C | O | N | R | A | D

2002 - 2004 REPORT

Making  
Progress  
Toward

**Better  
Reproductive  
Health**



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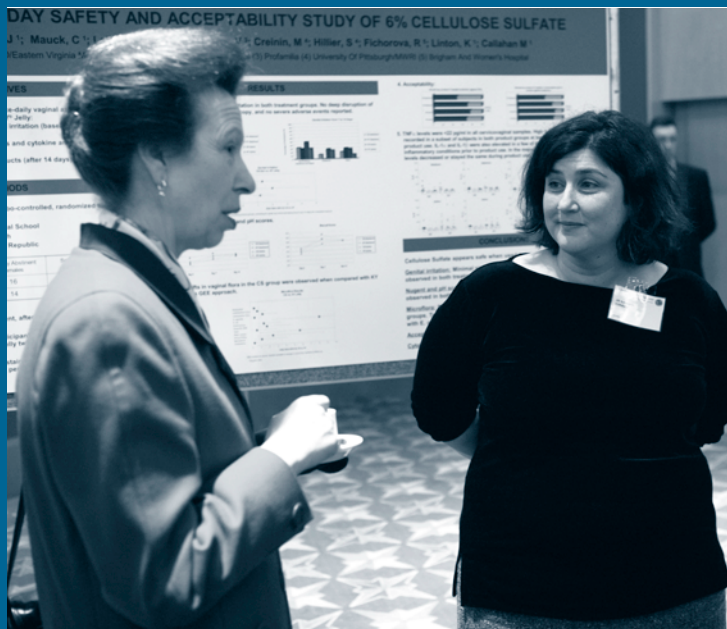
# Table of Contents

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3	Major Activities and Advances in 2002-2004
4	CONRAD's Mission
5	Main Challenges: Family Planning and HIV/AIDS
6	CONRAD's Funding
8	Research Activities by CONRAD, CICCR, and GMP
9	Methods for Women
9	Chemical Barriers
12	Mechanical Vaginal Barriers
14	CDC-Supported HIV/STI Prevention and Epidemiology Studies
14	Systemic Non-Hormonal Methods
16	Methods for Men
16	Systemic Hormonal Methods
17	Systemic Non-Hormonal Methods
19	Research Agenda
	Appendices
20	Selected Bibliography, 2002-2004
22	CONRAD-, CICCR-, and GMP-Supported Investigators, 2002-2004
31	Glossary of Abbreviations
32	CONRAD Staff

# C | O | N | R | A | D

CONRAD is committed to improving the reproductive health of men and women around the world by expanding their contraceptive choices and by helping to prevent the transmission of HIV/AIDS and other sexually transmitted infections (STIs).



The Princess Royal of England presents an award for microbicide research to Jill Schwartz of CONRAD at the Microbicides 2004 Conference in London.

# Major Activities and Advances in 2002-2004

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## **Chemical Barriers and HIV/STI Prevention**

CONRAD has played a leading role in the development of microbicides, which are topical agents that may protect their users from infection with HIV/AIDS and with other sexually transmitted pathogens. Cellulose sulfate (CS), a high molecular weight polymer developed by CONRAD, may prove to be a major advance in existing contraceptive technologies. Preclinical trials have already revealed the potential of CS to act as an effective guard against both unwanted pregnancies and STIs, including HIV/AIDS. Two Phase II contraceptive trials of CS were initiated in early 2004; Phase III HIV prevention trials will begin in late 2004 and in 2005 in countries with a high incidence of HIV infection, namely, in Nigeria (first trial) and in Benin, Burkina Faso, Uganda, South Africa, and India (second trial). CONRAD will continue to screen for novel safe and acceptable agents for use as vaginal microbicides and contraceptives.

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## **Mechanical Barrier Methods for Women**

CONRAD has a long history of supporting the development of mechanical vaginal barriers, with the objective of developing a "one-size-fits-all" device. It has supplied the developers of two intravaginal devices, Lea's Shield® and FemCap™, with the key clinical trial data required for Food and Drug Administration (FDA) approval. Lea's Shield, a one-size device, was approved by the FDA in 2002; FemCap, which was manufactured in three sizes to be fitted on the basis of a woman's obstetrical history, was approved by the FDA in 2003. CONRAD agrees with others in the field that the use of a mechanical barrier that covers the cervix should enhance the potential effectiveness of a microbicide product. CONRAD is, therefore, supporting several projects to explore the acceptability of using a diaphragm together with a microbicide gel, as well as the feasibility of including these combined products in an HIV prevention trial.

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## **Systemic Hormonal Methods for Men**

In search of effective and safe hormonal contraceptives for men, CONRAD has focused its efforts on hormonal methods involving a progestin/androgen combination. A contraceptive effectiveness trial of the combination of depot medroxy progesterone acetate (DMPA) plus testosterone (T) pellets was completed with no pregnancies occurring. However, the acceptability of this combination is probably not adequate for widespread use. Therefore, alternative combinations and delivery systems are desirable. CONRAD and the World Health Organization (WHO) have planned an expanded multicenter trial of a long-acting androgen/progestin combination (norethisterone enanthate plus testosterone undecanoate) to start in 2005.

# CONRAD'S Mission

**CONRAD is dedicated to improving reproductive health—particularly in developing countries where the need is greatest. Our goal is to develop better, safer, and more acceptable methods of contraception, and to help prevent the transmission of HIV/AIDS and other STIs.**

Established in 1986 under a cooperative agreement between Eastern Virginia Medical School and the U.S. Agency for International Development (USAID), CONRAD has been vigorously proactive in moving promising leads to clinical trials in the areas of contraception and in the prevention of STIs. Preclinical and clinical research on the safety and efficacy of potential new

**CONRAD is unique: it undertakes to move potential contraceptive/microbicide leads through all phases—from pre-clinical testing to the final product—for speedier development of products that are urgently needed.**

products is conducted at CONRAD's intramural facilities in Norfolk, Va., and in collaboration with investigators at universities, research institutions, and private companies worldwide.

CONRAD is unique in that it undertakes to move potential contraceptive/microbicide compounds through all of its phases—from preclinical testing, to clinical testing, to the final Phase III human testing, to providing the data to the FDA for approval, to collaborating with a manufacturing firm for the production of the final product. Such an "A-Z" process makes for a much speedier development of products that are urgently needed, as is the case in the current HIV/AIDS pandemic.



**Members of the CONRAD Intramural Preclinical Program lab at the Eastern Virginia Medical School in Norfolk, Va.**

# Main Challenges:

## Family Planning and HIV/AIDS

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### Family Planning

According to a report by the Global Health Council<sup>1</sup>, the world's 1.3 billion women between the ages of 15 and 45 had more than 1.2 billion pregnancies in the six years between 1995 and 2000. Of these, more than 300 million women, or more than one-quarter of all of the world's pregnancies, were unintended. Nearly 700,000 women died as a result of unintended pregnancies. Moreover, the number of women who risk unplanned pregnancies will grow as the world's population continues to rise. Over the next decade, 600 million girls are projected to reach adolescence, which will represent the largest world group of young women in human history.



The development of new effective and user-friendly contraceptives could help alleviate the growing unmet demand for satisfactory contraception and would certainly improve the lives of families everywhere, according to the Institute of Medicine<sup>2</sup>. At the same time, new global consortia working in this area are beginning to provide improved structures to facilitate and encourage collaborative work. Given the unprecedented opportunities for new progress in the field, now is the time to move forward with a bold research agenda.

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### HIV/AIDS

In 2004, over 37 million people worldwide were infected with HIV, the cause of AIDS. In 2003, almost 3 million people died of AIDS. During the 15th International AIDS Conference—the largest ever—held in July 2004 in Bangkok, Thailand, urgent calls were made for a focus on the prevention of HIV/AIDS. Prevention is considered the most important weapon in the fight against the pandemic. Progress reports were presented at the conference on a variety of approaches to prevention, such as vaccines, vaginal microbicides, and pills. The consensus view of the conference was that, although work on vaccines was expanding, an effective AIDS vaccine had not yet been developed. Many experts believed that a usable vaccine is at least 10 years off. However, closer to development is a microbicide that would protect a woman against infection acquired through sexual intercourse. The key is to give women a protective tool that they could control and one that they could initiate, if necessary. In many cultures, women find it difficult to negotiate condom use if their partner does not agree. In some parts of southern Africa, 25% of women were infected with AIDS by the time they turned 22 years of age. For women in many parts of the world, being poor, young, and married were the most significant risk factors for acquiring HIV infection.

<sup>1</sup>Global Health Council (2002). *Promises to Keep: The Toll of Unintended Pregnancies on Women's Lives in the Developing World*.

<sup>2</sup>Institute of Medicine (2004). *New Frontiers in Contraceptive Research—A Blueprint for Action*.

# CONRAD'S Funding

CONRAD is primarily funded by USAID, with additional funding provided from interagency agreements with the National Institute of Child Health and Human Development (NICHD), the Centers for Disease Control and Prevention (CDC), and the National Institute of Allergy and Infectious Diseases (NIAID).

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## **The Consortium for Industrial Collaboration in Contraceptive Research (CICCR)**

In 1995, CONRAD established the Consortium for Industrial Collaboration in Contraceptive Research (CICCR) to help revitalize the pharmaceutical industry's commitment to develop new contraceptives. CICCR promotes collaboration between not-for-profit entities and industry in the following three areas of research: methods for men, monthly regimens for women, and vaginal barriers that prevent pregnancy and STIs.

Funding for CICCR was initiated by the Rockefeller Foundation. Subsequent funding has also come from other private foundations: the Bill & Melinda Gates Foundation, the William and Flora Hewlett Foundation, the Andrew W. Mellon Foundation, the David and Lucile Packard Foundation, the United Nations Population Fund, and a foundation that wishes to remain anonymous.

### ***CICCR grants are awarded through three mechanisms:***

**Feasibility grants** support innovative, higher risk research. With this grant, a researcher can obtain preliminary results that would make a project more attractive to an industrial partner.

**Matching funds** are awarded to not-for-profit research institutions working in collaboration with for-profit industrial partners. Investigators applying for matching funds may have already secured industrial support, or may wish to find an industrial partner, also with CICCR assistance. Under this program, support is usually restricted to the early stages of drug development. Although funding is not restricted to matching on a 50:50 basis, preference is given to projects with a substantial level of industrial support. **The Twinning Program** has been solely funded by the Andrew W. Mellon Foundation. This program supports projects between investigators at Mellon-funded reproductive biology centers in the United States and selected research centers in developing countries.

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## **The Global Microbicide Project (GMP)**

In 2001, CONRAD established the Global Microbicide Project (GMP) to expedite the development of microbicides that may or may not be contraceptive, and that may be used as agents to fight sexually transmitted diseases, including HIV/AIDS. GMP provides funds for both pilot and major projects. Although there is no requirement for cost sharing by an industrial partner, such cost sharing is strongly encouraged. At present, funding for GMP comes solely from the Bill & Melinda Gates Foundation. Additional funds to investigate the contraceptive efficacy of microbicides and other agents are available through CICCR.

# Agreement of Cooperation on Microbicide Research Between

## **CONRAD and the Indian Council of Medical Research**

In August 2004, CONRAD and the Indian Council of Medical Research of New Delhi, India, signed a Memorandum of Understanding on cooperation in microbicide research. The principal objective of the agreement is to facilitate broad cooperation in the development of new, safe, and accessible methods of preventing the transmission of HIV/AIDS and of other STIs by means of microbicides, which would be suitable for use in developing countries. Both countries would benefit from this scientific and technological progress in the area of reproductive health.

The two institutes will cooperate in the following areas: drug discovery and formulation, preclinical screening, development of animal models, preparation of clinical sites to conduct microbicide research, and in the conduct of safety, effectiveness, and acceptability studies. CONRAD and the Indian Council of Medical Research have also agreed to exchange scientists and technical experts, as well as to exchange scientific and technological information, to jointly conduct research projects, to train young investigators, and to hold workshops, seminars and meetings.

The agreement was signed in New Delhi by Dr. Henry L. Gabelnick, Director of CONRAD, and Prof. Nirmal K. Ganguly, Director General of the Indian Council of Medical Research.

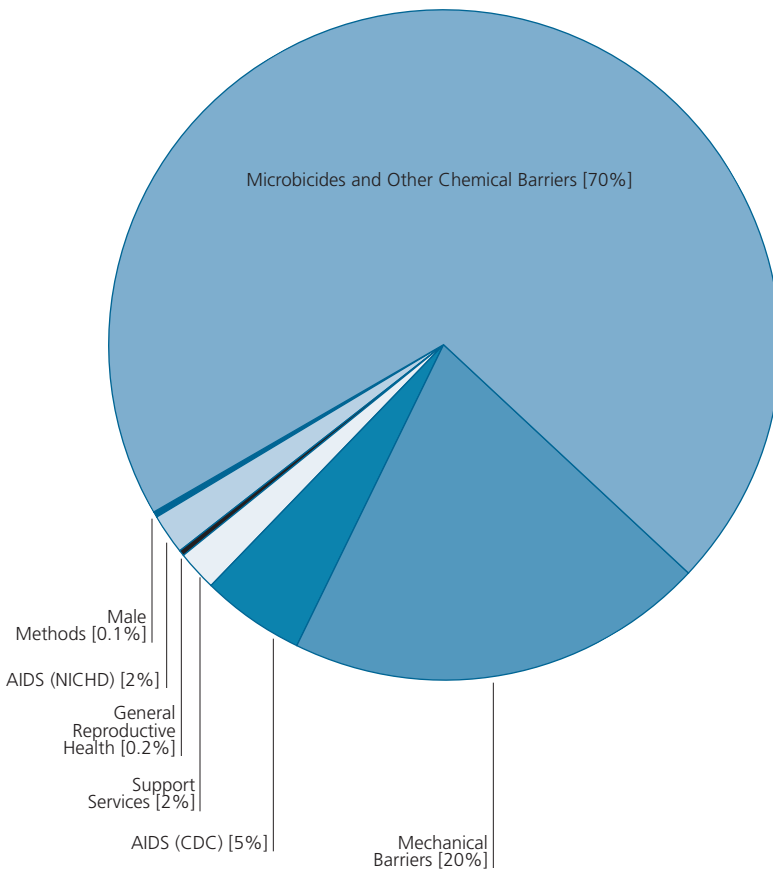
# Research Activities by CONRAD, CICCR, and GMP

CONRAD has made significant progress in supporting efforts to develop better, safer, and more acceptable methods to prevent pregnancy and STIs. These efforts have centered on five priority areas of research:

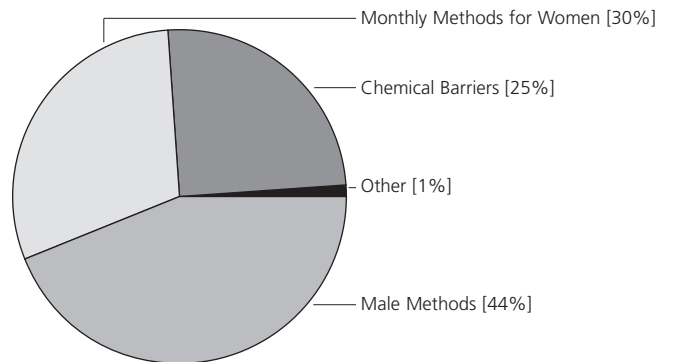
- Systemic contraceptive methods for women
- Systemic contraceptive methods for men
- HIV/STI prevention and epidemiology studies
- Chemical barriers that prevent pregnancy and STIs
- Mechanical barriers

## Projects Funded, 2002-2004

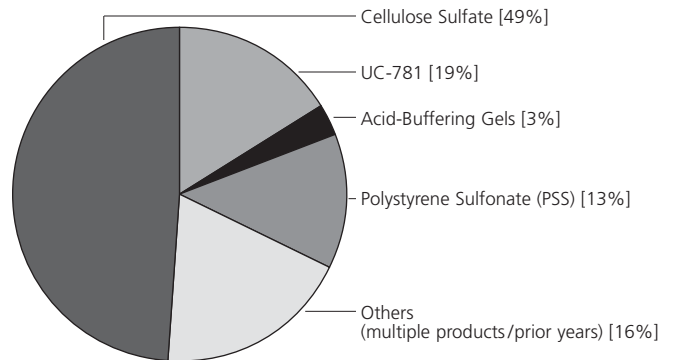
**CONRAD: \$13 million**  
(total extramural subproject awards)



**CICCR: \$7 million**



**GMP: \$8.1 million**



Note: Numbers do not total 100% due to rounding.



## Methods for Women

Expanding technologies that would protect women from pregnancy and from STIs is a key objective for CONRAD, as well as for its primary funding agency and its closest collaborator, USAID.

### Chemical Barriers

The development of chemical microbicides with or without contraceptive properties should be guided by the following criteria: The final product should allow women to control its use and provide effective levels of the drug at the target site. It should also minimize systemic exposure to the active ingredients, thereby minimizing potential adverse drug effects, and promote drug distribution and retention in the vaginal vault and over the cervix. The ideal product is one that is not messy, does not leak from the vagina, coats the whole vaginal surface rapidly, and has a prolonged action of at least 12 hours. The prolonged action would ensure that the product could be used privately by the woman, well ahead of the time when it was needed.

#### **Preclinical Studies of Chemical Barriers**

The goals of this program are to screen chemicals for safety and effectiveness against spermatozoal function and HIV infection, as well as against other sexually transmitted pathogens (STPs). Chemical compounds, such as microbicides, are assessed for contraceptive activity through multiple tests ranging from *in vitro* spermicidal assays to *in vivo* animal fertility trials, typically following an established algorithm. Screening is performed at CONRAD's Intramural Preclinical Program in its laboratories located at the Eastern Virginia Medical School, and through CONRAD'S collaborating laboratories.

CONRAD has developed novel *in vitro* and *in vivo* models to characterize the epithelial toxicity and proinflammatory potential of microbicide candidates. Given the enhancement of transmission registered when HIV encounters a disrupted, inflamed mucosa, assessment of these properties has become essential during both preclinical and clinical evaluation of these compounds. A network of investigators has been assembled with special expertise in a wide range of STIs. Such a network allows for *in vitro* and *in vivo* evaluation of a compound's effectiveness against the main STPs, including different strains and forms of HIV, herpes simplex virus, *Papilloma* virus, *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Treponema pallidum*, *Neisseria gonorrhoea*, *Gardnerella vaginalis*, *Haemophilus ducreyi*, and *Candida albicans*.

Several compounds identified through preclinical screening by CONRAD and by other organizations currently show promise as potential microbicides, with or without contraceptive activity, including cellulose sulfate (CS), BufferGel, ACIDFORM, polystyrene sulfonate (PSS),

Tenofovir (PMPA), naphthyl urea derivative (NUD), Z14, Savvy™ (C31G), UC-781, Carraguard™, PRO2000, and dextrin sulfate.

The two main acid-buffering formulations currently under evaluation in clinical trials are BufferGel and ACIDFORM. CONRAD is also currently conducting limited safety studies on lime juice, which is being actively promoted by others as a possible economical alternative for fighting STIs. The main purpose of these formulations is to counter the rise in vaginal pH caused by seminal plasma. The CONRAD Preclinical Program has conducted tests to compare the capacity of these compounds to lower the alkaline pH of seminal plasma, as well as their safety and activity.

### **Cellulose Sulfate (CS)**

Cellulose sulfate is one of the more promising microbicide leads supported by CONRAD, and, of the products in the CONRAD pipeline, it is the microbicide furthest along in development. The intellectual property rights to CS are owned by a Canadian company, Polydex Pharmaceuticals, which, through its subsidiary, Dextran Products, Ltd., has worked closely with CONRAD throughout the development process.

Preclinical trials have revealed the potential of CS to act as an effective guard against both unwanted pregnancies and STIs, including HIV, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and herpes simplex 1 and 2. Two Phase II contraceptive trials of CS started in early 2004. One is a “true efficacy” study being conducted with 150 couples by the California Family Health Council, in collaboration with CONRAD and Family Health International (FHI), to compare the risk of pregnancy during one menstrual cycle between two groups of women—one using either CS vaginal gel or a placebo gel formulation, with intercourse taking place during mid-cycle. The second is a Phase II contraceptive effectiveness trial also being conducted by the California Family Health Council. Two hundred couples will use a 3.5mL vaginal dose of 6% CS gel as their primary means of contraception for six months. The study objectives include: to determine the six-month typical-use pregnancy rate, and to measure the safety, adverse events, and acceptability of the CS gel. CONRAD/CICCR provided the main financial support for both of these contraceptive studies.

In the summer of 2004, the FDA gave permission for the first Phase III HIV prevention trial of CS to be carried out by FHI, in collaboration with CONRAD, at two sites in Nigeria. In October 2004, the FDA approved a second Phase III trial, which will begin in 2005 and will be conducted by CONRAD at six sites in Uganda, South Africa, India, Benin, and Bukino Faso—all regions with a high incidence of HIV infection. The two randomized placebo- controlled trials will assess the effect of 6% CS gel on HIV transmission among HIV-negative women who are at high risk of contracting HIV through heterosexual intercourse. The primary objective of the trials is to determine the effectiveness of CS gel compared to a placebo in preventing male-to-female vaginal transmission of HIV; the secondary objective is to determine the effectiveness of CS gel, compared to a placebo gel, in preventing male-to-female transmission of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.

### **Polystyrene Sulfonate (PSS)**

Polystyrene sulfonate (PSS) has proven to be effective against a growing number of STI organisms, such as HIV and herpes virus. A Phase I safety study was completed in 2001 at two clinical sites in the United States. Expanded safety studies (up to 14 days of PSS use) in men and women in the United States began in April 2003. Additional Phase I safety studies were expected to be initiated in HIV-positive women in Belgium by April 2003, in HIV-negative

women in India by the end of 2003, and in HIV-negative and -positive women by the end of 2003, with the support of WHO. However, in August 2003, in agreement with the FDA, CONRAD placed a hold on pursuing further clinical studies as a result of reproductive toxicology data in an animal model that needed to be further examined.

### **UC-781**

UC-781 is a nonnucleoside reverse transcriptase inhibitor being tested as a vaginal microbicide for the prevention of HIV transmission. CONRAD has completed the first Phase I safety trial of UC-781. The pharmaceutical company Biosyn has been working with CDC, as well as with CONRAD, to design a series of additional Phase I safety trials.

### **Acid-Buffering Gels: ACIDFORM and BufferGel**

ACIDFORM is a vaginal gel with a high buffering capacity that maintains vaginal pH below 4.5, even after seminal fluid deposition. CONRAD/GMP has supported the production of Phase I clinical supplies, as well as the evaluation of the safety of ACIDFORM gel, BufferGel, and K-Y® Jelly administered vaginally, and of ACIDFORM gel and K-Y Jelly used with a diaphragm. The company, Instead Inc., has licensed the rights for ACIDFORM from Rush-Presbyterian Medical Center.

### **Tenofovir**

The HIV Preventional Trials Network (HPTN) of NIH is conducting Phase I clinical studies with tenofovir, an antiviral nucleotide, to assess systemic absorption following intravaginal dosing. Tenofovir DF (Viread), which is a more bioavailable and biologically active pro-drug of tenofovir, is an orally active commercial antiretroviral agent. If vaginal tissue absorbs and retains tenofovir following vaginal administration, the drug could produce a long-acting depot effect. CONRAD is planning a Phase I pharmacokinetics (PK) study with vaginal tissue biopsies to investigate this possibility. A tenofovir bioanalytical method is being developed prior to the commencement of the PK study, to be validated with an *in vivo* rabbit and/or monkey vaginal dosing study.

### **Naphtyl Urea Derivative (NUD)**

Naphtyl urea derivative (NUD) displays contraceptive and antimicrobial properties. It inhibits growth and replication of several STPs. Regarding HIV and herpes viruses, it acts mainly as a viral entry inhibitor. NUD may also act through additional mechanisms because it inhibits viral RNA polymerase, chymotrypsin, kinases, and several growth factor receptors. NUD is non-cytotoxic and non-irritating to the cervicovaginal mucosa. It has been used in humans, systemically, as a preventative and therapeutic agent against certain parasitic infections. Absorption is very poor in humans via oral administration and in non-pregnant rats via intravaginal dosing (less than 1%). Intravaginal absorption in pregnant rats has also been shown to be <1%. Provided its vaginal absorption remains negligible, NUD is appealing as a vaginal microbicide.

### **Z-14**

The acylcarnitine analog Z-14 has demonstrated potent spermicidal and contraceptive activity, as well as potent virucidal activity against HIV-1 and HSV-2. Z-14 is highly active against other STPs. A more recent study of Z-14 in hydroxyethylcellulose has yielded a high rabbit vaginal irritation testing score; thus, alternative formulations that would be less irritating may be explored.

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**Mechanical  
Vaginal  
Barriers**

CONRAD has a long history of supporting the development of mechanical barriers. The objective is to develop a “one-size-fits-all” device. To expedite the process, a clinical development plan has been designed that varies somewhat, depending on the intrinsic qualities of the device. Preliminary evaluations include couples studies and studies to assess extended wear, slippage, breakage, and acceptability. Effectiveness as a contraceptive is evaluated initially in postcoital test studies and later in Phase II/III studies.

***Diaphragm Combinations***

Combining a physical barrier that covers the cervix with a spermicide/microbicide should enhance protection against STIs/AIDS and pregnancy. CONRAD is, therefore, supporting several projects to explore the feasibility of including the diaphragm in combination with a spermicide/microbicide in an HIV/STI prevention trial.

A study to assess whether female sex workers are willing and able to use the diaphragm plus K-Y Jelly for 6 months was recently carried out in Campinas, Brazil. A randomized, placebo-controlled safety study that will also assess the willingness of HIV-negative women, who are at low risk for STIs, to use a diaphragm plus either ACIDFORM gel or K-Y Jelly is ongoing in Johannesburg, South Africa.

The CDC, in collaboration with CONRAD, also is supporting a number of studies to explore the feasibility of adding a diaphragm in future microbicide effectiveness studies. A study to determine the compliance and acceptability of the standard latex diaphragm with lubricant among women who were unsuccessful in negotiating condom use with their partners in Zimbabwe has been completed. Results showed that more than half of the women used the diaphragm at least half of the time, and they liked using diaphragms more than they liked the use of condoms by their partners. More than 80% of the women did not always tell their partners that they were using the diaphragm. One hundred percent diaphragm use by women was associated with increased age, never using condoms, and never telling their partner that they used the diaphragm. These results indicated the feasibility of conducting a study in which the antimicrobial compound CS could be used in conjunction with a diaphragm in sexually active women for extended use. Such a study began in the fall of 2004 in Zimbabwe.

***Cervical Caps and Diaphragm-Like Devices***

The need for a perfect fit for diaphragm-like devices has recently been questioned in the context of ongoing STI prevention trials. A same-size device for all women would greatly simplify supplying the devices. An analysis of data from Lea’s Shield and from FemCap studies, comprising 1250 women, found that if all women were given one device of either size 65 mm, 70 mm, or 80 mm, then 78% of the women would be correctly fitted or else would receive a device that was only one size too large or too small. The clinical significance of providing a device which is one size (<1/4 inch) too big or too small is likely to be minor. It would, therefore, be feasible to carry out a study using a diaphragm of only one size.

**FemCap**

FemCap is a silicone rubber cervical cap that comes in three sizes. It has been modified from the original design by the addition of a removal strap. The FDA approved the device in 2003, based on CONRAD’s data as to FemCap’s clinical safety and effectiveness. The FemCap with strap will

be available by prescription only, and must be fitted by a clinician. It should be left in the vagina for at least six hours following intercourse, but for no longer than 48 hours. The probability of pregnancy, which was calculated from a Phase II/III study of women who used the original unstrapped device for six months, was 13.5%, and was extrapolated to 22.8% for 12 months of use of the device—compared to a probability of pregnancy of 7.9% and 17% for women using the diaphragm. The device's ability to reduce the risk of STIs or HIV has not been tested.

### **Lea's Shield**

Lea's Shield is a cup-shaped barrier device made of silicon rubber with a valve that allows the venting of air trapped between the cervix and the device, with a loop that aids in insertion and removal. The FDA approved Lea's Shield as a prescription-only device in March 2002, based on CONRAD's clinical data for safety and effectiveness. Lea's Shield is currently sold in Germany and Canada, and the developer plans to distribute it directly to clinicians in the United States. CONRAD plans to collaborate with FHI to conduct an acceptability study of Lea's Shield for dual protection from pregnancy and HIV/STIs.

### **SILCS Intravaginal Barrier Device**

The latest prototype of the SILCS intravaginal barrier device has included modifications, in order to accommodate more extremely flexed cervixes, to make insertion easier and more dependable for women who would wear larger than standard diaphragms (85 mm), to improve ease of removal, and to provide a better seal at key points of soft tissue. The one-size, reusable device was tested in 18 women for acceptability and fit in Seattle, and is being evaluated in a postcoital testing study in Norfolk and Pittsburgh. Acceptability, fit, and instructions will be assessed in a larger study in Thailand, the Dominican Republic, and South Africa. Once a "final" design meets expectations, CONRAD will collaborate with the Program for Appropriate Technology in Health (PATH) to complete the steps required for submission of the investigational device exemption to the FDA, and will also collaborate with FHI on the design of a contraceptive effectiveness study of the SILCS device.

### **Duet Device**

The BufferGel Duet, formerly called the BufferGel Cup, is a novel device designed to serve as a physical barrier and delivery vehicle for BufferGel or other microbicides. Biocompatibility, stability, and toxicity studies undertaken by the manufacturer have been completed successfully. CONRAD is supporting the development of manufacturing capability, in order to make enough of the product for initial clinical testing for acceptability, safety, and performance. The testing is scheduled to begin by the end of 2004.

### **Female Condoms**

CONRAD is also supporting efforts to develop an improved female condom. Initial evaluation of a non-latex prototype developed by PATH has been completed. The results led to the development of a second prototype, which is currently under clinical evaluation, with a unique attachment mechanism that should allow for a more universal fit. Final results from the comparative study of version 5 of the Reddy female condom and the Reality female condom showed that the Reddy condom had solved most of the functional problems associated with the device. Some modifications based on acceptability indicators are being explored in another clinical study of the Reddy condom. In addition, the Female Health Company has a

new version (FC2) of the only marketed female condom product, which CONRAD has agreed to test. A strategy is being developed by CONRAD, USAID, and FHI for these devices to be presented to the FDA, prior to initiating the next step in clinical development.

### ***Vaginal Product Assessment Technologies***

Colposcopy is becoming the accepted method to evaluate the effect of new vaginal products on the cervico-vaginal epithelium. However, still being investigated are: the most appropriate technique, the variability of findings between observers, the effect of the examination itself, the effect of non-product-related vaginal trauma, and the significance of the findings observed. Results of a CONRAD-sponsored colposcopy study found that colposcopic examination was not burdensome and did not induce iatrogenic findings. More findings were seen by using magnification than through the use of the naked eye. A similar number of findings were seen by AviScope, compared to the colposcope, but the Aviscope yielded more false-positive findings.

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### **CDC-Supported HIV/STI Prevention and Epidemiology Studies**

A CDC-supported study has been evaluating couples to determine the risk of HIV transmission to HIV-negative women from intrauterine insemination, using washed sperm from HIV-positive partners. The study is also evaluating the effect of the procedure on quality of life and sexual behavior. All participants reported that access to assisted reproductive care was difficult.

The influence of hormonal contraceptives and of other factors on HIV transmission has been studied among couples in Chiang Mai, Thailand. Couples were selected on the basis that the women remained HIV uninfected despite repeated contact with an HIV-positive husband. Factors associated with HIV progression and transmission amongst these discordant couples were investigated.

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### **Systemic Non-Hormonal Methods**

CONRAD/CICCR has also supported research on monthly methods for women. Research has focused on gonadotropin-releasing hormone action, signaling pathways such as angiogenesis, and other cytokines/growth factors that appear essential for pregnancy, such as interleukin-11 and the leukemia inhibitory factor. Because the biological processes involved in these signaling pathways are not well understood, it remains a difficult area of study. It is hoped that once an approach has proven successful, there will be more collaborative interest from the for-profit sector. The most interesting current projects in the field of monthly methods for women in the CICCR portfolio are:

#### ***Chicken II Gonadotropin-Releasing Hormone (GnRH) II***

It has been determined that there is a unique isoform of GnRH, called GnRH II, which has potent activity in reproductive tissues. An investigator in the United States has developed a novel analogue, which is resistant to metabolism and has much more potent activity on the reproductive tract than has mammalian GnRH. Studies in rhesus monkeys in China showed that when this analogue was given by minipump around the time of ovulation, pregnancy was inhibited in 17/17 animals over the entire dose range tested. This analogue can also be absorbed via the vagina in baboons, and can also interfere with ovarian function and possibly fertilization. Rapid progress of this compound to initial clinical trials is desired.

### ***Leukemia Inhibitory Factor (LIF)***

LIF was known to be essential for pregnancy in mice, but it was not certain if this was so for primates. A Chinese scientist was able to establish that instillation of a polyclonal antibody to LIF into the rhesus monkey uterus reduced pregnancy rates significantly. Further studies in

India with a monoclonal antibody were negative. Nevertheless, a peptide antagonist that binds LIF receptor (LIFR) was able to prevent pregnancy in mice, even though it was rapidly metabolized.

### ***Interleukin-11 (IL-11)***

IL-11 is a cytokine that appears to be intimately involved in the decidualization process in mice. Both the gene message and protein have been found to be highly expressed in human and monkey endometrium around the time of decidualization.

Similar technology to that for LIFR inhibitors is being used to make inhibitors of IL-11 receptor (IL-11R). One of these has also been shown to prevent pregnancy in mice. Here again rapid metabolism of the peptide is a problem.

### ***Novel Contraceptive Targets***

Together with the Ernst Schering Research Foundation and Schering AG, CONRAD/CICCR is co-sponsoring two programs that would target novel contraceptives. The first program, called the Application of Molecular Pharmacology for Post-Meiotic Activity (AMPPA-II), involves a network of investigators focused on novel epididymal and testicular targets. It is a continuation of a previous program co-sponsored by WHO and the Rockefeller Foundation. Seven institutes are receiving funding: the University of Newcastle, the Institute of Reproductive Medicine in Munster, Schering AG, the University of Virginia, the Blaise Pascal University, Vanderbilt Medical Center, and the Imperial College London/University of Turku.

The second program, Female AMPPA, has just been initiated. Four projects have been funded. One project deals with the regulation of ovulation; the second deals with determining endometrial gene expression by the use of microarrays; the third deals with studying the inhibition of an endometrial protease; and the fourth deals with developing a primate *in vitro* fertilization model for testing novel target molecules.

**Research on monthly methods for women has focused on gonadotropin-releasing hormone action, signaling pathways such as angiogenesis, and other cytokines/growth factors that appear essential for pregnancy, such as interleukin-11 and the leukemia inhibitory factor.**



## Methods for Men

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### Systemic Hormonal Methods

The ideal male contraceptive must not only be highly effective, but it must also produce minimal adverse effects, and it must be acceptable, suitable, and affordable to men in both developed and developing countries.

The most advanced studies on hormonal contraceptives for men involve regimens of androgen/progestin combinations that suppress gonadotropins and testicular testosterone production, thereby blocking spermatogenesis. Androgen/progestin combinations have been shown to induce azoospermia (the absence of sperm in the semen) or significant oligospermia (a deficiency in the number of sperm in the semen) more quickly than androgens alone. Progestins may also permit the use of less testosterone in the regimen, thereby reducing side effects such as acne, weight gain, or adverse effects on serum lipids, especially high-density lipoprotein cholesterol. None of the regimens currently under investigation appears to be ideal, but ongoing studies will direct research toward new and better methods. CONRAD continues to participate in studies to identify an optimal regimen with an acceptable method of delivery. Male contraceptive methods remain one of CICCR's research priority areas as well.

A contraceptive effectiveness study based on the combination of DMPA plus T pellets was conducted in Australia. There were no pregnancies in 426 couple months of exposure. Symptomatic androgen deficiency noted in a few men early in the study required increasing the frequency of T pellet replacement from every six months to every four months. In addition, DMPA injections were eliminated from the second half of the treatment phase because circulating MPA levels remained longer than expected. There were 27 discontinuations, 13 of which were related to the study drugs. Mean recovery time to normal sperm counts was 7-8 months, with some men taking 12 months.

During 2003, CONRAD/CICCR supported Phase I clinical studies of the production of GMP-grade testosterone microspheres as an alternative injectable long-acting androgen formulation. Although it was envisioned that additional studies of the T microspheres in combination with a progestagen would follow, the formulation had a low acceptability in the men tested. Also, the injection of the microsphere formulation was difficult in the prescribed injection volume.

CONRAD and WHO, in conjunction with several investigators around the world, continue to collaborate on the development of a male hormonal contraceptive. In mid-2003, Schering AG

confirmed the company's willingness to provide their long-acting injectable testosterone formulation, T undecanoate (TU), to use in combination with their long-acting injectable progestagen, norethisterone enanthate (NET-EN), for a multicenter contraceptive effectiveness trial. Preliminary pharmacokinetic dose finding studies of TU, with and without NET-EN, were ongoing in 2004, to determine the optimal dose for a contraceptive effectiveness trial. The multicenter contraceptive effectiveness trial based on bimonthly injections of TU plus NET-EN is expected to start in 2005 in several countries.

Alternative long-acting testosterone formulations will be pursued in 2005. The first is a newly developed T pellet by a U.S. manufacturer that will be tested in Phase I studies once clinical supplies become available. If pharmacokinetics and acceptability parameters are satisfactory, the pellets will be tested in combination with a long-acting progestagen.

In a collaborative study between Chinese and U.S. investigators funded by CICCR, four 200 mg T pellets were tested alone and in combination with four levonorgestrel (LNG) implants (two Norplant II systems). A total of 81 men were recruited into four study groups at each center. T pellets were replaced every 15 weeks to maintain androgen sufficiency. Of those receiving T pellets plus Norplant II rods, 70% of the non-Asian men achieved azoospermia by Week 18, and 85-90% of the Chinese men reached azoospermia by Week 21. As expected, sperm suppression was much less in the men who only received T pellets. T pellets were extruded in a few Chinese men. There were no changes in prostate volume and no clinically significant changes in serum lipids in any group of men.

### ***Progestagen Delivery Systems***

CONRAD is working with WHO and NICHD on the final development and manufacture of the long-acting formulation of the progestagen, LNG-butanoate. Once clinical supplies become available, CONRAD will conduct the Phase I pharmacokinetic studies in the CONRAD Clinical Research Center (CRC) in Norfolk. Also, an initial pharmacokinetic study of reformulated long-acting norethisterone (NET) pellets will be undertaken at the CONRAD CRC.

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### **Systemic Non-Hormonal Methods**

Preclinical investigations of systemic, non-hormonal approaches for male contraception are also underway, ranging from target identification and validation to efficacy testing in animal models. Because these approaches are in relatively early stages of development, CONRAD/CICCR feasibility and matching funds have been used to support these projects. In general, these approaches target sperm production or maturation in tissues of the male reproductive tract—testis, efferent ductules, and epididymis.

The most promising approaches involve agents that induce depletion and premature release of developing sperm from the testis. Two lonidamine analogs have demonstrated contraceptive efficacy and reversibility over a range of regimens in rats by investigators at the Population Council. Absorption studies of the lead candidate in rats revealed low bioavailability; therefore, the lead compound was micronized to increase bioavailability. Although acute toxicity studies were acceptable, dose-related adverse results were noted in a subchronic toxicity study. This resulted in the termination of further work on this lead by itself. Alternative delivery systems that would significantly decrease the amount of drug administered may be pursued.

An alternative approach under study is based on testis-selective delivery of peptide agents that would also deplete developing sperm from the testis by disrupting germ cell interaction with neighboring cells.

Since normal infertility depends on sperm maturation as they transit the epididymis, epididymal targets that are critical for sperm maturation and fertility are being identified. Targets being validated are androgen-dependent and present on the sperm surface. Male monkey immunogenicity studies have been conducted in India and Kenya, in which a number of different target immunogens were administered, including the epididymal protease inhibitor (Eppin), HE2 (Bin-1b), H42, cystatin 11, and others. When a group of male macaques that produced antibodies to Eppin were mated, no pregnancies occurred. This effect was reversible in most monkeys. Immunization did not affect sperm concentration or testosterone synthesis, but did result in modest effects on sperm function *in vitro*. These results served to validate

**The most promising approaches involve agents that induce depletion and premature release of developing sperm from the testis.**

Eppin as a potential target for male contraception, although methods to inhibit the biological effects of these antigens, such as Eppin, other than by antibody-based approaches, need to be identified.

The efferent ductules leading from the testis to the epididymis have a high concentration of estrogen receptors and are essential for fluid reabsorption. In small animal models, blocking the estrogen receptor in males by the oral administration of an anti-estrogen results in male infertility. However, testicular atrophy due to backpressure is a partial cause of this effect in rats (but not mice). Thus, treatment with an anti-estrogen was assessed in both dog and monkey models—whose efferent ductule structures are more similar to those in men—based on the hypothesis that diluting sperm as they enter the epididymis would result in abnormal maturation of sperm and in decreased sperm concentration. Perhaps due to the relatively high dose of anti-estrogen used, only a modest effect on dog sperm concentration was observed, and serum T levels were increased. Likewise, only modest effects on semen parameters in the bonnet monkey were observed. Alternative anti-estrogens are being studied.

# Research Agenda

CONRAD will continue to carry out its mandate for better reproductive health for all by increasing the contraceptive choices for women and men and preventing the spread of HIV/AIDS and other STIs. Over the next two years, CONRAD's top research priorities will be:

- Chemical barriers that protect women from pregnancy, HIV/AIDS, and STIs.
- Mechanical barriers for women that are acceptable and easy to use, and that can be combined with chemical gels to protect women against HIV/AIDS and against STIs.
- Systemic hormonal methods for men that are reversible and have minimal side effects.
- Novel systemic non-hormonal approaches for use by women and men.

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**CONRAD's key project objectives during the next two years include:**

## ***Microbicides and Other Chemical Barriers***

- Conduct Phase III effectiveness study of 6% CS for prevention of HIV/AIDS transmission.
- Evaluate the contraceptive effectiveness of 6% CS.
- Continue preclinical screening to identify new chemical vaginal contraceptive leads, and to further characterize compounds under development for contraceptive efficacy trials.
- Continue to identify safe and acceptable anti-HIV agents for use as vaginal microbicides, and to develop and characterize effective and marketable formulations for Phase II/III studies.
- Develop and validate *in vitro* and animal models for testing microbicidal safety and efficacy against HIV and other STPs.
- Develop clinical research centers outside the United States to perform vaginal/cervical colposcopy and STI laboratory testing, in association with expanded safety studies of candidate microbicides.
- Continue safety and clinical efficacy studies with lead compounds.
- Expand ongoing clinical studies of the standard diaphragm plus microbicides in order to prevent STIs (in collaboration with CDC).

## ***Mechanical Vaginal Barriers***

- Continue the development and clinical testing of intravaginal barrier devices (e.g., SILCS device and DUET).
- Continue clinical studies of two new female condoms—a non-latex prototype developed by PATH and the Reddy latex condom.

## ***Systemic Methods for Men***

- Collaborate with WHO on a large-scale, multicenter efficacy study of NET-EN plus TU.
- Pursue additional clinical studies involving more optimal androgen/progestin combinations and improved formulations.
- Continue preclinical development of non-hormonal leads through CONRAD's CICC program, and establish the feasibility of clinical testing in men.
- Continue to co-sponsor a program on the AMPPA-II with the Ernst Schering Research Foundation.

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# Investigators

## CONRAD-, CICCR-, and GMP-Supported Investigators, 2002-2004

<b>CONRAD-Supported Investigators, 2002-2004</b>	<b>INVESTIGATOR</b>	<b>INSTITUTION</b>	<b>PROJECT</b>
	<b>Michel Alary</b>	Centre Hospitalier Afflie Universitaire de Quebec QUEBEC, CANADA	Laboratory Upgrades in Contonou, Benin—Part I, and Colposcope Purchase
	<b>Deborah Anderson, Ph.D.</b>	Boston University School of Medicine BOSTON, MA	Cytokine Assessment in CVLs  Cervical Vaginal Lavage Evaluation for the ACIDFORM and Buffer Gel Study
	<b>Robert Anderson, Ph.D.</b>	Rush-Presbyterian- St. Luke's Medical Center CHICAGO, IL	TOPCAD Core Support
	<b>Glenn Austin</b>	Program for Appropriate Technology in Health SEATTLE, WA	Modification of SILCS Diaphragm  Development of a New Female Condom Using an Interactive Design Process: Phase II
	<b>Luis Bahamondes, M.D.</b>	CEMICAMP SAN PAULO, BRAZIL	An Acceptability and Feasibility Study of the Diaphragm and a Lubricant Gel Among Female Sex Workers
	<b>Kurt Barnhart, M.D., MSCE</b>	University of Pennsylvania Medical Center PHILADELPHIA, PA	The Optimal Analysis of MRI Data to Quantitate Distribution of a Vaginal Product  Safety Analysis of the Diaphragm in Combination with Vaginal Microbicide Gels  Vaginal Imaging Study of Replens and K-Y Jelly Using Three Imaging Techniques
	<b>Paul Blumenthal, M.D., M.P.H.</b>	The Johns Hopkins University BALTIMORE, MD	PATH Female Condom: Evaluation of Acceptability, Functional Performance, and Safety of the Double- Ring Design
	<b>Nigel Bourne, Ph.D.</b>	University of Texas Medical Branch HOUSTON, TX	Evaluation of Potential Microbicides Against HSV-2 and Chlamydia Trachomatis in Mice
	<b>Vivian Brache, Lic.</b>	PROFAMILIA SANTO DOMINGO, DOMINICAN REPUBLIC	Acceptability of SILCS Diaphragm Prototype 6
	<b>Anne Buve, M.D., Ph.D.</b>	Institute of Tropical Medicine ANTWERP, BELGIUM	Phase I 14-Day Safety and Acceptability Study of 10% Polystyrene Sulfonate Gel in HIV Positive Women  Male Tolerance Study of 6% Cellulose Sulfate Gel Following Multiple Topical Exposures in HIV Positive Men  Training for Laboratory Centers in PSS Study in India
	<b>Cecilia Cheng-Mayer, Ph.D.</b>	Aaron Diamond AIDS Research Center NEW YORK, NY	Refinement of the SHIV/Macaque Model for Use in Assessing Efficacy of Candidate Microbicides
	<b>Neil Christensen, Ph.D.</b>	Pennsylvania State University HERSHEY, PA	Evaluation of Potential Microbicides Against HPV and BPV

<b>Mitchell Creinin, M.D.</b>	Magee-Womens Health Corporation PITTSBURGH, PA	PATH Female Condom: Evaluation of Acceptability, Functional Performance, and Safety of the Double-Ring Design  A Phase I Comparative Postcoital Testing and Safety Study of the SILCS Diaphragm, Prototype VI
<b>Horacio Croxatto, M.D.</b>	Instituto Chileno de Medicina Reproductiva SANTIAGO, CHILE	Mechanism of Action of Post-Coital Levonorgestrel in Cebus Apella
<b>Laneta Dorflinger, Ph.D.</b>	Family Health International DURHAM, NC	Statistics and Data Management for "Safety Analysis of the Diaphragm in Combination with Vaginal Microbicide Gels" Study
<b>David Eschenbach</b>	University of Washington SEATTLE, WA	Formative Research of Diaphragm Use Among Sex Workers
<b>Raina Fichorova, M.D., Ph.D.</b>	Brigham and Women's Hospital BOSTON, MA	Refinement of the RVI Model and Detection of Proinflammatory Cytokines in Animal and Human Vaginal Lavage  Development of <i>In Vitro</i> Tests for Preclinical Assessment of Proinflammatory Side Effects of Vaginal Microbicides
<b>Ron Freziers, MSPH</b>	California Family Health LOS ANGELES, CA	Comparative Research Study of the Reality Female Council Condom and Version 4 of the Reddy Female Condom  Comparative Research Study of the Reality Female Condom and Version 5 of the Reddy Female Condom
<b>Richard Gandour, Ph.D.</b>	Virginia Polytechnic Institute and State University BLACKSBURG, VA	Multi-Headed Anionic Surfactants as Potential Topical Microbicides
<b>David Grimes, M.D.</b>	Family Health International RESEARCH TRIANGLE PARK, NC	North America Coordinating Site of the Fertility Regulation Group of the Cochrane Collaboration
<b>David Handelsman, M.D., Ph.D.</b>	Royal Prince Alfred Hospital SYDNEY, AUSTRALIA	Efficacy, Safety, and Service Feasibility of an Androgen/Progestin Depot Regimen for Hormonal Contraception
<b>Betsy Herold, M.D.</b>	Mount Sinai Medical Center NEW YORK, NY	<i>In Vitro</i> Evaluation of Potentially Microbicidal Agents for Anti-HSV Activity
<b>Sharon Hillier, Ph.D.</b>	Magee-Womens Health Corporation PITTSBURGH, PA	A Phase I Dose-Ranging Study of the Safety and Colonization Efficiency of Lactin-V Administered Intravaginally to Healthy Women  Gram Stain Evaluation for the ACIDFORM and Buffer Gel Phase I Study
<b>Ann Jerse, Ph.D.</b>	Uniformed Services University BETHESDA, MD	Blocking Transmission of Neisseria Gonorrhoeae in a Mouse Model
<b>David Katz, Ph.D.</b>	Duke University DURHAM, NC	Vaginal Imaging Study of Replens and K-Y Jelly Using Three Imaging Techniques
<b>Fred Krebs, Ph.D.</b>	Pennsylvania State College of Medicine HERSHEY, PA	<i>In Vitro</i> Evaluation of Test Agents for Anti-HIV Activity
<b>John Lewicki, Ph.D.</b>	Osel, Inc. SANTA CLARA, CA	Preclinical and Phase I Studies of Lactin-V
<b>Richard Markham, M.D.</b>	The Johns Hopkins University BALTIMORE, MD	Evaluation of Candidate Microbicides in Immunodeficient Mice Reconstituted with Human Peripheral Blood Mononuclear Cells (PBMCs)

<b>Lois Martin, Ph.D.</b>	Tulane National Primate Research Center COVINGTON, LA	A Defined Model for Vaginal Transmissions of SIV/SHIV in Cynomolgus Monkeys ( <i>Macaca fascicularis</i> )
<b>Thomas R. Moench, M.D.</b>	ReProtect, LLC BALTIMORE, MD	Development of BufferGel Cup  Development of Thin Wall Molding Fabrication Method for BufferGel Cup  Manufacturing of BufferGel for the HPTN 035 HIV Prevention Trial
<b>Kenrad Nelson, M.D.</b>	The Johns Hopkins University BALTIMORE, MD	Survival of HIV-1 Infected Male Blood Donors and Their Infected Partners in Northern Thailand
<b>Julie Omohundro</b>	DURHAM, NC	Regulatory Consulting and QA Audits of Clinical Trials
<b>Nancy Padian, Ph.D.</b>	University of California SAN FRANCISCO, CA	Acceptability of Diaphragm Use in Zimbabwe  Phase I Safety Trial of Diaphragm plus Microbicide in Zimbabwe
<b>Dorothy Patton, Ph.D.</b>	University of Washington SEATTLE, WA	Chlamydia Trachomatis plus SHIV: Co-Infection Model Development in the Pig-Tailed Macaque
<b>Adrian Puren, MBBCh., Ph.D.</b>	National Institute for Communicable Diseases JOHANNESBURG, SOUTH AFRICA	Safety and Feasibility Study of the Diaphragm Used with ACIDFORM Gel or KY Jelly
<b>Haleh Sangi-Haghpeykar, Ph.D.</b>	Baylor College of Medicine HOUSTON, TX	Psychosocial Predictors of Condom Use Among Injectable Contraceptive Users
<b>Badri Saxena, M.D., F.A.M.</b>	NEW DELHI, INDIA	CONRAD Consultant for US-Indo Microbicides Projects
<b>Augusto Semprini, M.D.</b>	ESMAN Medical Consulting, s.r.l. MILAN, ITALY	Risk of Infection with HIV-1 in Women Inseminated with Their HIV-1 Infected Partner's Processed Semen and in Children Conceived by this Method: A Retrospective, Ongoing Study
<b>Alan Stone, Ph.D.</b>	Medical Scientific Advisory Services LONDON, ENGLAND	IWGM Services as Chariman
<b>Tangie Thomas</b>	ATLANTA, GA	Contract Monitoring and QA Audits of Clinical Trials
<b>Guido Vanham</b>	Institute of Tropical Medicine ANTWERP, BELGIUM	A Two-Chambered System of Epithelial Cells and Dendritic Plus CD4 T-Cell Co-Cultures to Test Candidate Microbicides
<b>Christina Wang, M.D.</b>	Harbor-UCLA Research and Education Institute TORRANCE, CA	Comparison of the Efficacy of a Progestagen Implant (Norplant II) in Combination with Transdermal Androgen versus Transdermal Androgen Alone in Suppression of Spermatogenesis in Normal Men  Comparison of Efficacy of Suppression of Spermatogenesis with Progestagen Implant (Norplant II) and Androgen Implants (T Pellets) versus Androgen Implants Alone in Asian and Non-Asian Men
<b>Lourens Zaneveld, Ph.D.</b>	Rush-Presbyterian-St. Luke's Medical Center CHICAGO, IL	Development and Evaluation of Novel Vagina Antimicrobial Contraceptive Formulations

**CICCR-  
Supported  
Investigators,  
2002-2004**

<b>INVESTIGATOR</b>	<b>INSTITUTION</b>	<b>PROJECT</b>
<b>Frank Alvarez, M.D.</b>	PROFAMILIA SANTO DOMINGO, DOMINICAN REPUBLIC	Phase I Clinical Trial of the LNG Regimen: Effects of Timing of Administration Within the Follicular Phase on the Leading Follicle, Hormone Levels, and Adverse Events
<b>Robert Anderson, Ph.D.</b>	Rush-Presbyterian- St. Luke's Medical Center CHICAGO, IL	Biological Tests with CONRAD Compounds  Pre-NDA Development of Cellulose Sulfate as a Contraceptive Antimicrobial Product
<b>Manuel Baca, B.Sc. (Hons), Ph.D.</b>	The Walter and Eliza Hall Institute of Medical Research MELBOURNE, AUSTRALIA	Discovery of Peptidic Antagonists of Leukemia Inhibitory Factor by Phage Display
<b>Vivian Brache, Lic.</b>	PROFAMILIA SANTO DOMINGO, DOMINICAN REPUBLIC	Phase 1 Clinical Trial of the Effect of Levonorgestrel in Combination with Cyclooxygenase-2 Inhibitor on the Ovulatory Process
<b>William Bremner, M.D, Ph.D.</b>	University of Washington SEATTLE, WA	Assessment of Bimonthly Regimen of Injectable TU and DMPA for Contraception on Chinese Men
<b>Yi-Qun Gu, M.D.</b>	National Research Institute for Family Planning BEIJING, P.R. CHINA	
<b>C. Yan Cheng, Ph.D.</b>	The Population Council NEW YORK, NY	Development of Peptide-Based Male Contraceptives that Disrupt Adhesion of Germ Cells onto the Seminiferous Epithelium
<b>C. Yan Cheng, Ph.D.</b>	The Population Council NEW YORK, NY	Induction of Release of Premature Germ Cells from Seminiferous Epithelium by Analogs of Lonidamine
<b>Bruno Silvestrini, M.D., Ph.D.</b>	Fondazione di NOOPOLIS ROME, ITALY	
<b>C. Yan Cheng, Ph.D.</b>	The Population Council NEW YORK, NY	Development of Novel Male Contraceptives
<b>Austin Cooney, Ph.D.</b>	Baylor College of Medicine HOUSTON, TX	Evaluation of the Contraceptive Effects of GCNF Ligands
<b>Austin Cooney, Ph.D.</b>	Baylor College of Medicine HOUSTON, TX	Multihormonal Effects of 19-nor Contraceptive Synthetic Progestins: An Approach to Design Steroid Agonists/Antagonists
<b>Fernando Larrea, M.D.</b>	Instituto Nacional de la Nutricion Salvador Zubiran MEXICO D.F., MEXICO	
<b>Horacio Croxatto, M.D.</b>	Instituto Chileno de Medicina Reproductiva SANTIAGO, CHILE	Synergistic Effect of RU486 and the Aromatase Inhibitor Letrozole on the Inhibition of Pregnancy in the New World Monkey  Phase I Clinical Trial of the LNG Regimen: Effects of Timing of Administration Within the Follicular Phase
<b>Patricia Cuasnicu, Ph.D.</b>	Instituto de Biologia y Medicina Experimental BUENOS AIRES, ARGENTINA	Potential Contraceptive Use of an Epididymal Protein
<b>Paul Primakoff, Ph.D.</b>	University of California DAVIS, CA	
<b>Ron G. Frezieres, MSPH</b>	California Family Health Council, Inc. LOS ANGELES, CA	True Contraceptive Efficacy of Cellulose Sulfate— A Randomized Controlled Trial
<b>Markus Steiner, Ph.D.</b>	Family Health International DURHAM, NC	

<b>Ron G. Frezieres, MSPH</b>	California Family Health Council, Inc. LOS ANGELES, CA	Non-Comparative Contraceptive Effectiveness Trial of Cellulose Sulfate (CS) Gel
<b>Robert E. Garfield, Ph.D.</b>	University of Texas Medical Branch GALVESTON, TX	Synergistic Effects of Mesoproggestins and Antiproggestins with iNOS and COX-2 Inhibitors on the Inhibition of Pregnancy
<b>George Gerton, Ph.D.</b>	University of Pennsylvania PHILADELPHIA, PA	Identification of Zona Pellucida-Derived Small Molecule Effectors of Sperm Function
<b>Fernando Larrea, M.D.</b>	Instituto Nacional de al Nutricion Salvador Zubiran MEXICO, D.F., MEXICO	
<b>Susan Hall, Ph.D.</b>	University of North Carolina CHAPEL HILL, NC	Human Epididymal Protein Targets for Male Contraception
<b>A. Jagannadha Rao, Ph.D.</b>	Indian Institute of Science BANGALORE, INDIA	
<b>Susan Hall, Ph.D.</b>	University of North Carolina CHAPEL HILL, NC	Androgen and Estrogen Regulation of Contraceptive Target Gene Expression in Epididymis of the Bonnet Monkey, Macaca Radiate
<b>John C. Herr, Ph.D.</b>	University of Virginia CHARLOTTESVILLE, VA	Human Testicular Soluble Adenylyl Cyclase as a Target for Contraception
<b>Vrinda Vijay Khole, Ph.D.</b>	Institute for Research in Reproduction MUMBAI, INDIA	
<b>Rex Hess, Ph.D.</b>	University of Illinois at Urbana-Champaign URBANA, IL	Use of Antiestrogens for Contraception in the Male
<b>Joan Hunt, Ph.D.</b>	University of Kansas Medical Center KANSAS CITY, KS	Paan-AG as a Contraceptive Target in Baboons
<b>Joan Hunt, Ph.D.</b>	University of Kansas Medical Center KANSAS CITY, KS	Biochemical and Molecular Characterization of an HLA-G-like Gene Expressed in Baboon (Papio anubis) Placentas
<b>Jason Mwenda, Ph.D.</b>	Institute for Primate Research NAIROBI, KENYA	
<b>Malini Laloraya, Ph.D.</b>	School of Life Sciences, Bangalore INDORE, INDIA	Contraceptive Effect of Antiproggestins RU-486 and Cabergoline in Relation to Their Effects on the Expression of 32.6 kDa Progesterone-Induced Protein
<b>Bill Lasley, Ph.D.</b>	University of California DAVIS, CA	Imuno-Neutralization of Leukemia Inhibitory Factor as an Anti-Implantation Strategy
<b>Yi-Xun Liu, M.D.</b>	Chinese Academy of Sciences BEIJING, P.R. CHINA	A Chicken II Gonadotropin-Releasing Hormone Analog as a Lutolytic, Menses-Inducing Agent or a Postcoital Contraceptive
<b>Alvin Matsumoto, M.D.</b>	University of Washington SEATTLE, WA	Pharmacokinetics, Pharmacodynamics, Acceptability and Safety of Testosterone Microcapsule Injections in Normal Men
<b>Robert McLachlan, M.D., Ph.D.</b>	Prince Henry's Institute of Medical Research CLAYTON, AUSTRALIA	Serum Gonadotropin Levels During Male Hormonal Contraception: Relevance of the Degree of Gonadotropin Suppression to Azoo- versus Oligospermic Responses
<b>Cristina Meriggiola, M.D.</b>	University of Bologna BOLOGNA, ITALY	Pharmacokinetics of Testosterone Undecanoate Injected Every 8 Weeks with Norethinsterone Enanthate, 200mg, in Healthy Men

<b>Dolores Mruk, Ph.D.</b>	The Population Council NEW YORK, NY	Design, Characterization, and Development of Novel Glutathione Analogs as Contraceptives
<b>Chandrima Shaha, Ph.D.</b>	National Institute of Immunology NEW DELHI, INDIA	
<b>Tarala Nandedkar, Ph.D.</b>	Institute for Research in Reproduction MUMBAI, INDIA	Evaluation of Antifertility Effect of FSH-Binding Inhibitor
<b>Maria Elena Ortiz</b>	Instituto Chileno De Medicina Reproductiva SANTIAGO, CHILE	A Feasibility Study on the Transduction of Endometrial Cells and the Role of Lefty on Implantation
<b>Siamak Tabibzadeh, M.D.</b>	The Research Foundation of State University of New York MANHASSET, NY	
<b>James W. Overstreet, M.D., Ph.D.</b>	University of California DAVIS, CA	Immuno-Neutralization of Leukemia Inhibitory Factor as an Anti-Implantation Strategy
<b>Jayasree Sengupta, Ph.D.</b>	All India Institute of Medical Sciences NEW DELHI, INDIA	
<b>Paul Primikoff, Ph.D.</b>	University of California DAVIS, CA	Potential Contraceptive Use of an Epididymal Protein
<b>John Rasweiler</b>	SUNY Downstate Medical Research Center BROOKLYN, NY	Development of a Better Animal Model for the Study of Human Implantation
<b>Lorraine Robb, MBBS, BSc(Hons), Ph.D</b>	Walter and Eliza Hall Institute for Medical Research MELBOURNE, AUSTRALIA	Investigation in the Role of Interleukin-11 in Human Female Fertility
<b>Lois Salamonsen, Ph.D.</b>	Prince Henry's Institute of Medical Research CLAYTON, AUSTRALIA	Inhibition of LIF and Interleukin-11 as a Contraceptive Strategy; Application of Newly Developed Antagonists
<b>Gerald Schatten, Ph.D.</b>	Magee-Womens Health Corporation PITTSBURGH, PA	Acrosome Biogenesis as a Target for Contraception
<b>Ricardo Moreno, Ph.D.</b>	Instituto Chileno de Medicina Reproductiva SANTIAGO, CHILE	
<b>Jaysree Sengupta, Ph.D. Debabrata Ghosh, Ph.D.</b>	All India Institute of Medical Sciences NEW DELHI, INDIA	Effect of Fumagillin and Magainins on Blastocyst Implantation in the Rhesus Monkey
<b>James Overstreet, M.D., Ph.D.</b>	University of California DAVIS, CA	
<b>Jayasree Sengupta, Ph.D.</b>	All India Institute of Medical Sciences NEW DELHI, INDIA	Involvement of Epithelial Membrane Protein (EMP2) in Blastocyst Implantation in the Rhesus Monkey
<b>Chandrima Shaha, Ph.D.</b>	National Institute of Immunology NEW DELHI, INDIA	Functional Inhibition of a 24 kDa Molecule with Glutathione S-Transferase Activity (for Male Contraception)
<b>Theresa Siler-Khodr, Ph.D.</b>	Center for Investigation of Cell Regulation and Replication SAN ANTONIO, TX	Gonadotropin-Releasing Hormone Analogs as a Luteolytic, Menses-Inducing Agent or a Postcoital Contraceptive
<b>Bruno Silvestrini, M.D., Ph.D.</b>	Gondazione di NOOPOLIS ROME, ITALY	Development of a Novel Male Contraceptive

<b>Bruno Silvestrini, M.D., Ph.D.</b>	Gondazione di NOOPOLIS ROME, ITALY	Synthesis of AF-2364
<b>Anil Suri, Ph.D.</b>	National Institute of Immunology NEW DELHI, INDIA	Isolation and Characterization of Genes Encoding Sperm Surface Antigens by Screening Human Testis cDNA Libraries
<b>Ronald Swerdloff, M.D., Ph.D.</b>	Harbor-UCLA Medical Center TORRANCE, CA	Combined Effects of Hormone and Heat Treatment on the Suppression of Spermatogenesis in Men: Proof of the "Two-Hit" Concept  Testicular Gene Regulation by Hormone and Heat Treatment in Men
<b>Paul Terranova, Ph.D.</b>	University of Kansas Medical Center Research Institute KANSAS CITY, KS	The Role of Intra-Oocyte Src Family Tyrosine Kinase on Fertilization-Induced Mouse Oocyte Activation
<b>Luis Velasquez, Ph.D.</b>	Instituto Chileno de Medicina Reproductiva SANTIAGO, CHILE	Comparison of Gene Expression in the Endometrium During the Receptive Period in Women Who Were Refractory to Implantation in Repeated Cycles of Oocyte Donation and Women Who Got Pregnant in the Same Program
<b>Christina Wang, Ph.D.</b>	Harbor-UCLA Research and Education Institute TORRANCE, CA	Pharmacokinetics of Testosterone Undecanoate Injections in Healthy Men
<b>Carmen Williams, M.D., Ph.D.</b>	University of Pennsylvania PHILADELPHIA, PA	Tetraspan Protein Function in Primate Implantation
<b>Zengming Yang, Ph.D.</b>	Northeast Agricultural University HARBIN, P.R. CHINA	Effects of Systemic Administration of Anti-leukemia Inhibitory Factor Antibody and Thalidomide on Monkey Implantation

<b>GMP- Supported Investigators, 2002-2004</b>	<b>INVESTIGATOR</b>	<b>INSTITUTION</b>	<b>PROJECT</b>
	<b>Michel Alary</b>	Centre Hospitalier Afflie Universitaire de Quebec QUEBEC, CANADA	Preparatory Phase for the Randomized Controlled Trial of 6% Cellulose Sulfate Gel and the Effect on Vaginal HIV Transmission Study
	<b>Kurt Barnhart, M.D., MSCE</b>	University of Pennsylvania Medical Center PHILADELPHIA, PA	A Phase I Comparative Postcoital Testing and Safety Study of Three Concentrations of C31G
	<b>Vivian Brache, Lic.</b>	PROFAMILIA SANTO DOMINGO, DOMINICAN REPUBLIC	Vaginal Imaging Study of 2.5 ml CS versus 3.5 ml CS
	<b>Mitchell Creinin, M.D.</b>	Magee-Womens Health Corporation PITTSBURGH, PA	Phase I 14-Day Safety and Acceptability Study of 6% Cellulose Sulfate
	<b>Lynn Bradley, M.Sc.</b>	Johns Hopkins Medical Service Corporation BALTIMORE, MD	Phase I 14-Day Safety and Acceptability Study of ACIDFORM Gel
	<b>Mitchell Creinin, M.D.</b>	Magee-Womens Health Corporation PITTSBURGH, PA	
	<b>Michael Thomas, M.D.</b>	University of Cincinnati CINCINNATI, OH	
	<b>Mitchell Creinin, M.D.</b>	Magee-Womens Health Corporation PITTSBURGH, PA	Phase I 14-Day Safety and Acceptability Study of 10% PSS
	<b>Alfred Poindexter, M.D.</b>	Advances in Health, Inc. HOUSTON, TX	
	<b>Mitchell Creinin, M.D.</b>	Magee-Womens Health Corporation PITTSBURGH, PA	Phase I Comparative Postcoital Testing and Safety Study of Three Concentrations of C31G
	<b>Laneta Dorflinger, Ph.D.</b>	Family Health International DURHAM, NC	Collaboration Agreement for Support of Joint Microbicide Projects
	<b>Anibal Faundes, M.D.</b>	CEMICAMP SAN PAULO, BRAZIL	Postcoital Testing and Vaginal Ecology After Use of a Bioadhesive Acid Buffering Gel
	<b>Ron G. Frezieres, MSPH</b>	California Family Health Council LOS ANGELES, CA	Male Tolerance Study of 10% PSS Gel Following Multiple Topical Exposures
	<b>Kenneth Mayer, M.D.</b>	The Miriam Hospital PROVIDENCE, RI	
	<b>Ron G. Frezieres, MSPH</b>	California Family Health Council LOS ANGELES, CA	Male Tolerance Study of C31G Following Multiple Topical Exposures
	<b>Sanjay Garg, Ph.D.</b>	National Institute of Pharmaceutical Education and Research PUNJAB, INDIA	Bioadhesion and Retention Properties of CS, PSS, and ACIDFORM Formulations: Method Development and Validation
		School of Pharmacy, University of Auckland AUCKLAND, NEW ZEALAND	Development of Fast-Dissolving Vaginal Tablets of Sodium Cellulose Sulfate
	<b>Jerry Gromelski, Ph.D.</b>	MDS Pharma Services MONTREAL, CANADA	Suramin Absorption Studies in Rat
	<b>Ellen Hardy, Ph.D.</b>	Centro de Pesquisas Materno- Infantis de Campinas CAMPINAS, BRAZIL	Evaluation of Women's Experience with the Use of Different Vaginal Formulations: Pilot Study

<b>Polly Harrison, Ph.D.</b>	Alliance for Microbicide Development SILVER SPRING, MD	Alliance for Microbicide Development: Program of Work 2001-2003  Alliance for Microbicide Development: Program of Work for 2004
<b>Ian McGowan, M.D.</b>	UCLA Center for HIV and Digestive Diseases LOS ANGELES, CA	Development of Protocol to Investigate the Safety and Tolerability of Rectally Administered Cellulose Sulfate
<b>Frances Mielach, Ph.D., R.P.H.</b>	Aspen Biomedical Consulting, Ltd. BETHESDA, MD	Toxicology Monitoring of Cellulose Sulfate
<b>Richard Olson</b>	R.A. Olson Associates Strategies for Business Growth BLOOMFIELD, NJ	Business Development Consultation on Manufacture of Polystyrene Sulfonate (PSS)
<b>Alfred Poindexter, M.D.</b>	Advances in Health, Inc. HOUSTON, TX	Male Tolerance Study of ACIDFORM Gel Following Multiple Topical Exposures
<b>Albert T. Profy, Ph.D.</b>	Indevus Pharmaceuticals LEXINGTON, MA	Nonclinical Toxicity Evaluation of PRO 2000/5 Gel: A Candidate Vaginal Microbicide
<b>Danny J. Schust, M.D.</b>	Brigham and Women's Hospital BOSTON, MA	Testing Vaginal Microbicide Formulations for Lymphocyte Activation and Viability
<b>Jose A. Simoes, M.D., Ph.D.</b>	Centro de Pesquisas Materno-Infantis de Campinas CAMPINAS, BRAZIL	Comparison Between ACIDFORM and Metronidazole for the Treatment of Bacterial Vaginosis: A Pilot Clinical Trial
<b>Eric Smart</b>	Organichem Corporation RENSSELAER, NJ	Manufacture of Sodium Cellulose Sulfate
<b>Esther Thompson</b>	Family Health International DURHAM, NC	Statistics and Data Management for CONRAD Protocol #A00-062
<b>Kyle T. Vanderlick, Ph.D.</b>	Princeton University PRINCETON, NJ	Boosting and Targeting the Action of Surface-Active Microbicides
<b>Donald P. Waller, Ph.D.</b>	University of Illinois CHICAGO, IL	Establishment of a Center for Microbicide Research in India
<b>Dong Xie, Ph.D.</b>	Frontier Biotechnologies Co, Ltd. CHONGQING, CHINA	Preformulation Study of HIV Fusion Inhibitors FB006 and FB006M

# Glossary of Abbreviations

<b>AIDS</b>	acquired immune deficiency syndrome
<b>AMPPA-II</b>	Application of Molecular Pharmacology for Post-Meiotic Activity
<b>CDC</b>	Centers for Disease Control and Prevention
<b>CICCR</b>	Consortium for Industrial Collaboration in Contraceptive Research
<b>CRC</b>	CONRAD Clinical Research Center (Norfolk, Va.)
<b>CS</b>	cellulose sulfate
<b>DMPA</b>	depot medroxy progesterone acetate
<b>EPPIN</b>	epididymal protease inhibitor
<b>FDA</b>	Food and Drug Administration
<b>FHI</b>	Family Health International
<b>GMP</b>	Global Microbicide Project
<b>GnRH</b>	gonadotropin-releasing hormone
<b>HIV</b>	human immunodeficiency virus
<b>HPTN</b>	HIV Prevention Trials Network
<b>IL-11</b>	interleukin-11
<b>LIF</b>	leukemia inhibitory factor
<b>LNG</b>	levonorgestrel
<b>NET</b>	norethisterone
<b>NET-EN</b>	norethisterone enanthate
<b>NICHD</b>	National Institute of Child Health and Human Development
<b>NIAID</b>	National Institute of Allergy and Infectious Diseases
<b>NUD</b>	naphtyl urea derivative
<b>PATH</b>	Program for Appropriate Technology in Health
<b>PK</b>	pharmacokinetic
<b>PSS</b>	polystyrene sulfonate
<b>T</b>	testosterone
<b>TU</b>	testosterone undecanoate
<b>STI</b>	sexually transmitted infection
<b>STP</b>	sexually transmitted pathogen
<b>WHO</b>	World Health Organization
<b>USAID</b>	U.S. Agency for International Development

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