

Healthy Women, Healthy Nations



2006 - 2007 REPORT

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LEADERS IN REPRODUCTIVE HEALTH AND HIV PREVENTION

CONRAD REPORT
2006 - 2007

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In 2005, more than half of the estimated five million people who contracted HIV worldwide were young people aged 15 to 24, the majority of them young women and girls. The economic effect of such devastating diseases is enormous. In South Africa, HIV/AIDS can reduce GDP growth by as much as 20 percent. *World Bank World Development Report 2007*

Letter from the Executive Director

Imagine a world in which each and every child is not only wanted and cared for but is healthy and strong. Imagine a world in which a mother can be confident that her children will live to see their teenage years or a young couple can feel secure in making choices about when to have children.

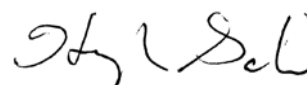
The reality for many men and women around the world is far different. It is estimated that 33.2 million people are infected with HIV. Today, young people aged 15 to 24 account for more than half of all new HIV infections, and teenage girls – our future mothers – become infected at twice the rate of boys. In 2003, there were an estimated 15 million orphans due to AIDS around the world and that number is expected to increase to 25 million by 2010 (UNAIDS 2002).

Complications from pregnancy and childbirth are the leading cause of death in young women aged 15 to 19 in developing countries and an estimated 70,000 adolescent mothers die each year because they have children before they are physically ready for parenthood. Early pregnancy and pregnancies without adequate spacing contribute not only to disease and mortality but also to widespread poverty. When women and men have access to improved reproductive health, not only do their families thrive, but their communities are strengthened.

It is known that women face an extraordinarily high risk of exposure to HIV/AIDS, and serious lasting physical damage, if not death, from unintended pregnancies. Often isolated in communities lacking basic necessities, they are without knowledge of their options for better reproductive health, or the means to access them. Now more than ever, sexual and reproductive health programs must play a critical role in prevention, care, and treatment of HIV/AIDS.

The development of safe, acceptable and affordable products to prevent HIV infection and pregnancy is essential for the health of our women, our nations and our future. Indeed, in many parts of the world, entire economies are rising or falling on their government's ability to protect its citizens from the scourge of HIV/AIDS, rising infant mortality rates, and deaths from unintended pregnancies.

We dare to envision a world where every person has control of his or her reproductive life, a world freed from the scourge of HIV/AIDS and from the needless suffering and death caused by unintended pregnancy.



Henry Gabelnick, PhD
Executive Director





Photo courtesy of Stephanie Combes

CONRAD's Mission :

CONRAD's overall goal is to improve reproductive health, especially in developing countries. Our main objective is to help develop safe, acceptable, affordable products and methods that provide contraception and/or prevent the sexual transmission of HIV/AIDS and other infections.

We accomplish this by :

Nurturing promising research in institutions worldwide

Engaging in preclinical research

Conducting clinical trials

Partnering with private industry to get new products on the market

Collaborating with other agencies, foundations, and non-governmental organizations

Training investigators throughout the world in preclinical and clinical research techniques.

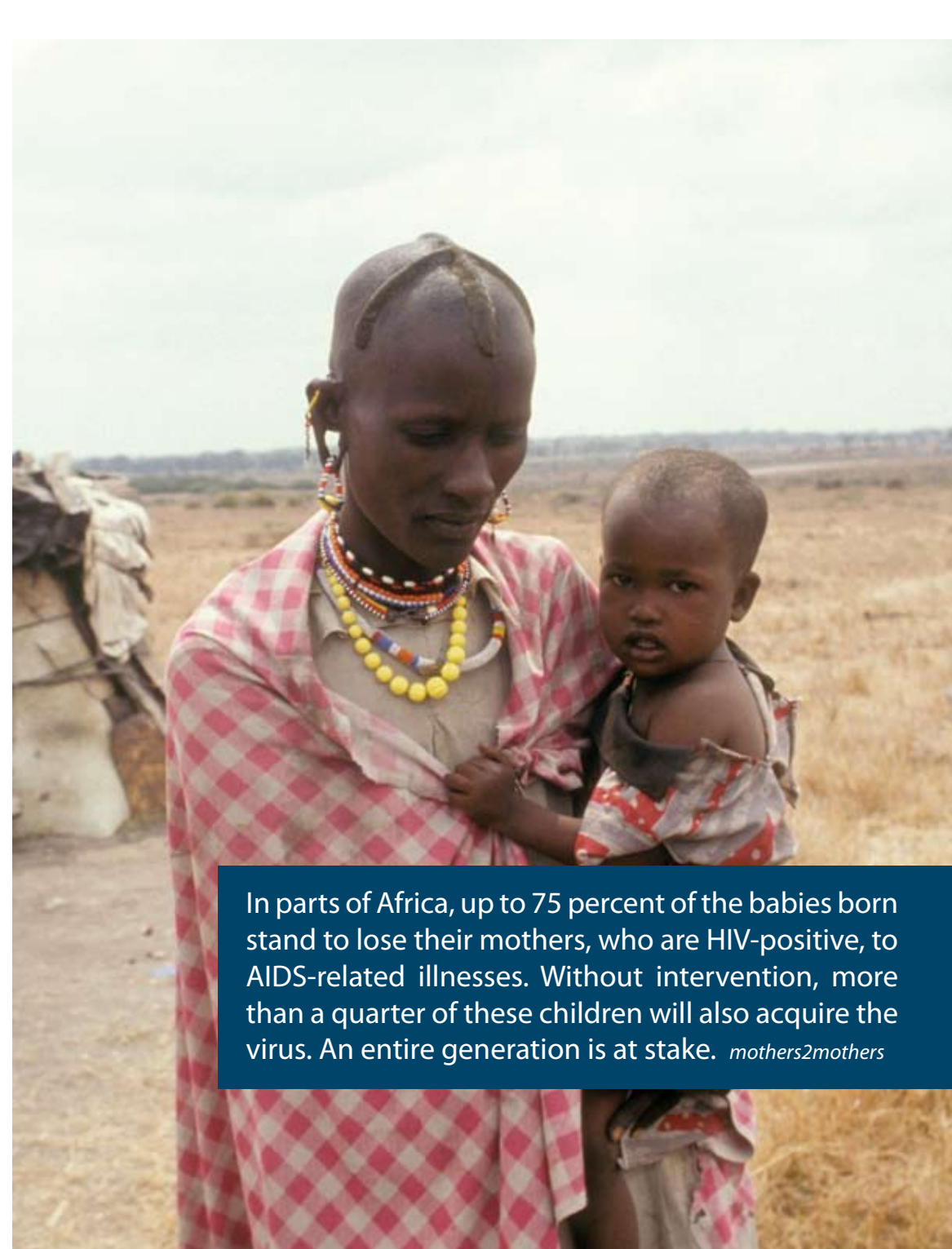
CONRAD's Approach to Microbicide Research

For over twenty years, CONRAD has served as a resource for the microbicide field as a whole. As a leader in research, both at the preclinical and clinical level, we've accumulated a wealth of experience that is contributing to the development of a safe and effective microbicide. Our scientists have helped advance several microbicide candidates currently in clinical trials, including PRO2000, BufferGel, tenofovir and UC781.

The uniqueness of CONRAD has been critical to getting microbicide development where it is today. We have helped advance several microbicide candidates currently in clinical trials, including PRO2000, BufferGel™, tenofovir, and UC781.

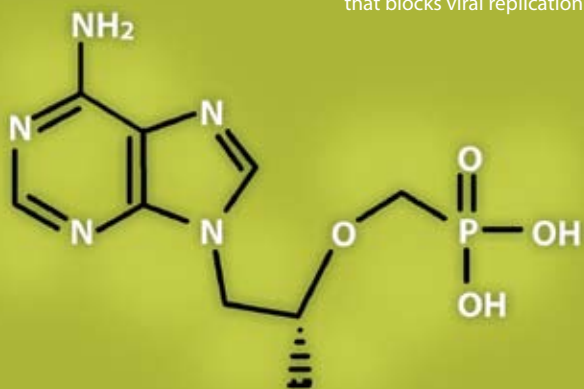
With funding received over the past twelve years from the Bill & Melinda Gates Foundation, USAID, and other sources, we developed cellulose sulfate (CS) through the preclinical and early clinical research stages to the stage of Phase III clinical trials. CS has displayed great promise as a contraceptive. Contrary to all expectations and available data, CS failed to protect women exposed to a high risk of contracting HIV. We are currently engaged in a thorough scientific effort to try to ascertain the possible biological causes for that failure. As disappointing as these results are, they provide us with the unique opportunity to learn more about the sexual transmission of HIV and validate models and biomarkers of microbicide safety and efficacy.

CONRAD has pioneered research in microbicide safety, both at the preclinical and clinical level, and remains a leader in this area. Due to integrated, in-house, preclinical and clinical research teams, we have the capacity to take a novel biomarker all the way from discovery to clinical validation. This is a unique strength of the program, which is now reinforced by our ability to work with compounds that have failed in phase III clinical trials.

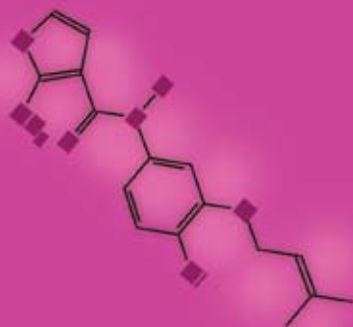


In parts of Africa, up to 75 percent of the babies born stand to lose their mothers, who are HIV-positive, to AIDS-related illnesses. Without intervention, more than a quarter of these children will also acquire the virus. An entire generation is at stake. *mothers2mothers*

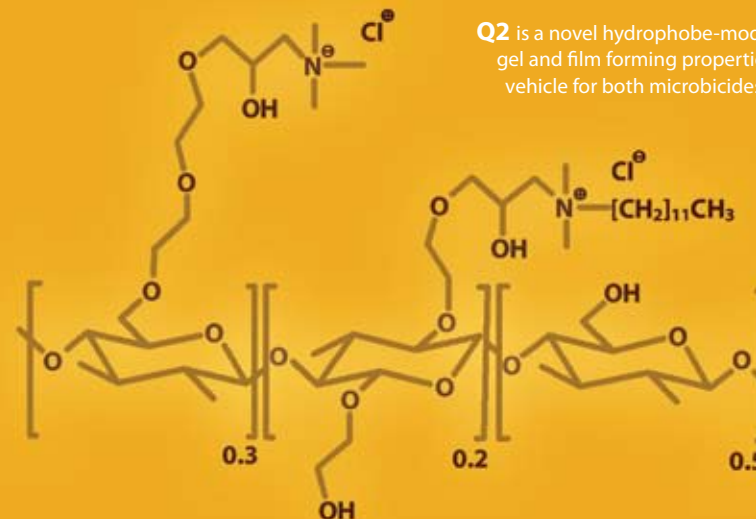
Tenofovir is a nucleotide reverse transcriptase inhibitor (NRTI) that blocks viral replication.



UC781 is a non-nucleotide reverse transcriptase inhibitor (NNRTI) that blocks viral replication.



Q2 is a novel hydrophobe-modified, cationic polymer with gel and film forming properties. It will be used as a novel vehicle for both microbicides and contraceptive agents.



Microbicide Mechanisms of Action

Killing or inactivating pathogens

Virucides disable the virus by breaking up its surface membrane or envelope or by inactivating key viral receptors or enzymes. If they are membrane-active compounds, they can also disable sperm, thereby acting as effective contraceptives. The challenge in this case is to make sure that virucides are specific enough to disrupt the invading pathogen, but without damaging the healthy cells that line the vaginal walls.

Strengthening the body's normal defenses

This approach builds or improves upon what the body already does to protect itself. For example, a healthy vagina is normally acidic, which makes it inhospitable to invading pathogens like HIV. But semen counteracts this acidity, creating an environment where HIV can survive. Some candidate microbicides build on the simple principle of maintaining the vagina's natural acidity even in the presence of semen.

Inhibiting viral entry

Entry inhibitors work by interfering with the virus getting into the body's white blood cells, the target cells of HIV. There are two categories of entry inhibitors: attachment inhibitors that prevent attachment of the virus to white blood cells and fusion inhibitors that prevent HIV from actually entering cells.

Antiretroviral

Some candidate microbicides are being developed from the antiretroviral drugs that HIV-positive people use to lower the amount of virus in their bodies. Formulated as gels or creams, these drugs may be able to suppress replication of any HIV that enters the vagina or rectum during sex. If so, they could substantially lower the odds that the microbicide user will become infected.

Cellulose Sulfate Gel

Cellulose sulfate (CS) is a cotton-based compound that was formulated as a clear gel for clinical studies. A CONRAD-initiated Phase II trial of CS in 200 couples showed that CS functioned well as a contraceptive, with a six-month typical use pregnancy probability of 13.4% and a “perfect use” rate of 3.9%.

In vitro, CS also helps prevent HIV from entering the target cells. CS inhibits cell entry and multiplication of other sexually transmitted infection pathogens such as herpes virus, papilloma virus, and chlamydia.

Scientists scrutinized the safety data from 11 clinical studies conducted on CS in Africa, Europe, India and the United States. None of the data suggested that the product could increase the susceptibility to HIV and, in fact, results from the contraceptive trial suggested that it could possibly prevent infection.

Two Phase III trials of CS as a microbicide began in 2006, one in Nigeria conducted by Family Health International (FHI) and the other in Benin, South Africa, Uganda and India. A planned interim analysis of the CONRAD study data, presented to an independent data monitoring committee, showed that CS might be contributing to an increased risk of HIV infection. Although the number of seroconversions was small, the group in the CS arm of the study contracted HIV at higher rates than did those in the placebo arm, and therefore the trial was stopped. FHI subsequently decided to close its CS study in Nigeria due to the safety concerns raised in the CONRAD trial, even though the interim results from the FHI study did not show an increased risk of HIV infection among women using CS. Final results, which were presented at the International AIDS Society conference in Sydney, Australia, showed that the difference in HIV seroconversions between the CS group and the placebo group was not statistically significant.

Following the halt of the study, scientists from CONRAD conducted a study of CS in two groups of six monkeys each to try to understand why the microbicide was not effective in women. A placebo was used in one group, while 6% CS gel was used in the second group.



Although 5/6 macaques were infected in the placebo group, none of the animals in the CS gel group seroconverted. These data suggest that consistent vaginal application of CS gel effectively reduced the infectivity of the virus, significantly decreasing the rate of vaginal mucosal SHIV transmission following repeated virus exposures.

Why does CS have a protective effect on monkeys and not in humans? There is not a clear explanation at this point. However, certain hypotheses are plausible. Women may not have consistently used the gel with every act of intercourse. They used the gels more frequently than in the monkey study, possibly irritating the vaginal mucosa or changing its microflora. Although scientifically sound, the monkey model has not been clinically validated yet and may differ from the actual human conditions of transmission in a way that affects its predictive power.

In spite of extensive preclinical characterization proving CS safety and efficacy, the CS-containing gel tested in Phase III clinical trials failed to effectively protect women from acquiring HIV infection. Comprehensive additional research is currently ongoing to try to verify hypotheses about the causes for such failure. The need for better, more predictive preclinical models and clinical biomarkers of microbicide safety and efficacy is evident.

CONRAD's Global Work

CONRAD's work in developing new contraceptive products and microbicides takes the form of research studies conducted across the globe.

Identification and development of new microbicides, including development and validation of small animal models for HIV and formulation work are ongoing by investigators, collaborators and contractors in **Germany, Northern Ireland, and the Dominican Republic.**

Similarly, the Phase II effectiveness trial of the combination of an androgen and a progestin for male contraception is being conducted in collaboration with WHO (Switzerland) by investigators in **Italy, Germany, Chile, Australia, United Kingdom, Indonesia and India.**

With support from the Hewlett Foundation, CONRAD initiated a dose-finding trial in **Chile** to show that meloxicam has the potential to be used as an emergency contraceptive. This followed up initial probing studies in **Chile** and **Jordan** verifying that it could prevent ovulation by itself and enhance the effect of levonorgestrel (the presently recommended emergency contraceptive treatment).

In Pune, **India**, CONRAD joined forces with the National AIDS Research Institute of the Indian Council of Medical Research to investigate the effects of the menstrual cycle on colposcopic findings on the cervix. Additionally, the Medtech Products female condom has been tested in India.

CONRAD is providing supplies of the antiretroviral tenofovir for an ongoing Phase IIb clinical trial for HIV prevention in **South Africa**. The trial is being conducted by CAPRISA.

In both **Thailand** and **Atlanta**, CONRAD is working with CDC on safety studies focusing on the antiretroviral UC781 for use as a microbicide.

In January 2008, in six cities of the **United States**, CONRAD began a Phase III contraceptive trial of the SILCS diaphragm, together with FHI and in collaboration with PATH.

While the Phase III trial of cellulose sulfate for HIV prevention – held in **Benin, South Africa, Uganda and India** – concluded early due to lack of efficacy, the trial helped pave the way for research on new safe and effective microbicides.



Major Activities and Advances in 2006-2007

Microbicides

Antiretrovirals as microbicides: tenofovir

Partner: International Partnership for Microbicides

CONRAD, along with the International Partnership for Microbicides, has been granted a co-exclusive license in developing countries for tenofovir by Gilead Sciences. Monkey and rabbit pharmacokinetic studies were conducted prior to initiating a pharmacokinetic study in women in March, 2007. The clinical portion of this study was completed in April 2008. A male tolerance study of tenofovir gel was carried out in 2006. Clinical supplies are being manufactured under CONRAD's supervision for a Phase IIb clinical trial in South Africa that is ongoing.

Antiretrovirals as microbicides: UC781

Partners: CDC and NIH

UC781 is a tight-binding non-nucleoside reverse transcriptase inhibitor (NNRTI) with excellent anti-HIV microbicidal properties, showing high potency alone and in drug combinations. CONRAD has licensed UC781 from Cellegy and Chemtura for development and public-sector marketing. Safety studies are underway in collaboration with CDC at Emory University in Atlanta and in Thailand. A male tolerance study was initiated by CONRAD at the California Family Health Council in Los Angeles, while a rectal safety study was launched at the University of California, Los Angeles, and a pharmacokinetic study which was conducted at the University of Pittsburgh.

Enhancing the predictive power of preclinical evaluation of microbicide efficacy

An improved rabbit vaginal irritation model that provides information on the pro-inflammatory potential of microbicide candidates has been developed. In combination with in vitro tests, this model has enhanced the predictive power of preclinical evaluation.

New markers of mucosal inflammation have been identified and assessed in preclinical studies and are currently being validated in clinical trials. Development of low-dose, multiple-challenge SHIV and high-dose RT-SHIV vaginal infection models in monkeys is underway. Progress has also been made toward establishing small-animal models that are susceptible to HIV vaginal infection, and which will be useful for the early evaluation of microbicide efficacy.



Marriage is proving to be a serious risk factor for HIV infection for women. Studies in Kenya and Zambia have shown that younger married women are at a higher risk of HIV infection than their unmarried counterparts. *UNIFEM Facts & Figures on HIV/AIDS 2004*



Major Activities and Advances in 2006-2007

Microbicides

TESTING THE VIRUCIDAL QUALITIES OF TRADITIONAL REMEDIES

CONRAD completed a trial of intravaginal lime juice which took place in response to reports of Nigerian women applying lemon or lime juice intravaginally around the time of intercourse, due to a belief that it would protect them against HIV and other sexually transmitted infections. Preclinical data suggested that lime juice might be an active virucide, but only in high concentrations that are likely to be cytotoxic. In this prospective clinical trial, women were randomized to apply either water or lime juice (25%, 50%, or undiluted) intravaginally twice daily for two six-day intervals, separated by a three-week washout period. During one interval, they applied their product using a saturated tampon and during the other by douche, in order to simulate, as much as possible, practices in the field. Among the observations were a dose-dependent pattern of symptoms, gross physical examination findings, colposcopic findings of deep epithelial disruption, and changes in some inflammatory markers that were consistent with a compromised vaginal barrier function. The largest drop in pH was about one half of a pH unit, seen one hour after douching with 100% lime juice. It was felt that this brief reduction in pH was highly unlikely to be virucidal in the presence of semen, which transports HIV. The conclusion was that lime juice is unlikely to protect against HIV and may be harmful. Results from this careful prospective clinical investigation were reported at the Microbicides 2006 meeting in South Africa in order to reach a wide audience.

The significance of the menstrual cycle on colposcopic findings on the cervix

*Partner: National AIDS Research Institute of the
Indian Council of Medical Research*

A study that investigated the effects of the menstrual cycle on colposcopic findings on the cervix was conducted in Pune, India, in collaboration with the National AIDS Research Institute of the Indian Council of Medical Research. It concluded that the mean diameter of the largest visible blood vessel differed significantly between the estrogenic and progestogenic phases, and that such changes observed during the progestogenic phase in safety studies should be considered normal.

International conference on biomarker research

Partner: Alliance for Microbicide Development

In collaboration with the Alliance for Microbicide Development, CONRAD organized a conference in November 2006 that presented the state of the art in biomarker research applied to microbicide development. Almost 100 participants from industry, academia, and non-governmental and governmental organizations discussed biomarkers of semen exposure, cervico-vaginal inflammation and HIV infection. This conference was the first of its kind and helped to identify gaps in knowledge, as well as studies and possible collaborations to resolve these gaps. Proceedings will be published in an open-access journal.

Inflammatory markers

A study of inflammatory markers in women using vaginal products was begun at two sites. Women are being randomized to use 14 days of twice-daily applications of a hydroxyethylcellulose-based "universal" placebo, 6% cellulose sulfate, or 4% nonoxynol-9 (Conceptrol®) gel. New safety endpoints are being studied that include soluble and cellular markers of inflammation in cervico-vaginal lavage fluid, biopsy specimens, and cytobrush specimens, as well as changes in pH, vaginal microflora, colposcopic findings, histopathological measures, and antiviral activity of the CVL supernatant. The degree of correlation between different methods of clinical assessment being used in the trial will be determined, as will the degree of correlation between the results of this clinical study and the results of the preclinical assessment of the same compounds.



Women's lack of control over their own fertility keeps millions of them mired in poverty...if the World Bank is serious about ending poverty, it needs to enhance women's ability to make independent choices about having children.
LaShawn R. Jefferson, women's rights director at Human Rights Watch

2006-2007 Microbicide Research	Description	Status	Partner
<p>ANTIRETROVIRALS: TENOFOVIR CONRAD and the International Partnership for Microbicides have licensed tenofovir from Gilead for continued clinical development .</p>	<p>Monkey and rabbit pharmacokinetic studies were conducted prior to initiating a pharmacokinetic study in women in March of 2007. A male tolerance study of tenofovir gel was carried out in 2006.</p>	<p>The pharmacokinetic clinical portion of this study conducted at Magee-Womens Research Institute (Pittsburgh), Advances in Health (Houston) and PROFAMILA (Dominican Republic) will be completed by April 2008. Clinical supplies are being manufactured under CONRAD's supervision for a Phase IIb clinical trial in South Africa that is ongoing.</p>	<p>International Partnership for Microbicides</p>
<p>ANTIRETROVIRALS: UC781 CONRAD has licensed UC781 from Chemtura for development and public-sector marketing.</p>	<p>UC781 is a tight-binding non-nucleoside reverse transcriptase inhibitor (NNRTI) with excellent anti-HIV microbicidal properties, showing high potency alone and in drug combinations.</p>	<p>Safety studies are underway in collaboration with CDC at Emory University in Atlanta and in Thailand. A male tolerance study was initiated by CONRAD at the California Family Health Council in Los Angeles, while a rectal safety study was launched at the University of California, Los Angeles, and a pharmacokinetic study commenced at the University of Pittsburgh.</p>	<p>CDC and NIH</p>
<p>PRECLINICAL EVALUATION New and improved models to assess microbicide safety and efficacy.</p>	<p>An improved rabbit vaginal irritation (RVI) model that provides information on the pro-inflammatory potential of microbicide candidates has been developed. In combination with in vitro tests, this model will enhance the predictive power of preclinical evaluation.</p> <p>New markers of mucosal inflammation have been identified and assessed in preclinical studies and are currently being validated in clinical trials.</p> <p>Models to assess microbicide efficacy are also being developed.</p>	<p>The improved RVI is being used to evaluate candidates that failed in phase III clinical trials and those that are currently in development</p> <p>Development of low-dose, multiple-challenge, R5/X4 SHIV and high-dose RT-SHIV vaginal infection models in monkeys is underway.</p> <p>Progress has also been made toward establishing small-animal models that are susceptible to HIV vaginal infection, and which will be useful for the early evaluation of microbicide efficacy.</p>	<p>None</p>
<p>TESTING TRADITIONAL REMEDIES CONRAD recently completed a trial of intravaginal lime juice.</p>	<p>This trial took place in response to reports of Nigerian women applying lemon or lime juice intravaginally around the time of intercourse, believing that it would protect them against vaginal acquisition of HIV and other sexually transmitted infections.</p>	<p>Among the observations were a dose-dependent pattern of symptoms, gross physical examination findings, colposcopic findings of deep epithelial disruption, and changes in some inflammatory markers that were consistent with a compromised vaginal barrier function. The conclusion was that lime juice is unlikely to protect against HIV and may be harmful.</p>	<p>None</p>
<p>STUDYING THE MENSTRUAL CYCLE A study that investigated the effects of the menstrual cycle on colposcopic findings on the cervix was conducted in Pune, India, in collaboration with the National AIDS Research Institute of the Indian Council of Medical Research.</p>	<p>It was concluded that the mean diameter of the largest visible blood vessel differed significantly between the estrogenic and progestogenic phases, and that such changes observed during the progestogenic phase in safety studies should be considered normal.</p>	<p>Completed</p>	<p>National AIDS Research Institute of the Indian Council of Medical Research</p>
<p>BIOMARKER RESEARCH A conference took place in Reston, Virginia of November 2006 that presented the state of the art in biomarker research applied to microbicide development. Discussions focused on biomarkers of semen exposure, cervico-vaginal inflammation and HIV infection.</p>	<p>This conference was the first of its kind and helped to identify gaps in knowledge, as well as studies and possible collaborations to resolve these gaps.</p>	<p>Proceedings are being written up and will be published in an open-access journal.</p>	<p>Alliance for Microbicide Development</p>
<p>INFLAMMATORY MARKERS A study of inflammatory markers in women using vaginal products was begun at two sites.</p>	<p>Women are being randomized to use 14 days of twice-daily applications of a hydroxyethylcellulose-based "universal" placebo, 6% cellulose sulfate, or 4% nonoxynol-9 (Conceptrol®) gel. New safety endpoints are being studied that include soluble and cellular markers of inflammation in CVL fluid, biopsy specimens, and cytobrush specimens, as well as changes in pH, vaginal microflora, colposcopic findings, histopathological measures, and antiviral activity of the CVL supernatant.</p>	<p>The degree of correlation between different methods of clinical assessment being used in the trial will be determined, as will the degree of correlation between the results of this clinical study and the results of the preclinical assessment of the same compounds.</p>	<p>None</p>



Biomarkers

One of the strengths of our program is our capacity to take a novel biomarker from discovery to clinical validation. Biomarkers are biochemical substances that can be used to measure the progress of disease or the effects of treatment. In the area of vaginal product research, biomarkers could give early information about the safety and likely efficacy of both contraceptive and microbicide products, facilitating triage of less promising candidate products. In addition, biomarkers of sexual behavior and study product use could help with interpretation of study results. As examples, CONRAD is developing new biomarkers of cervicovaginal inflammation, indicating safety or lack of it, and new biomarkers of vaginal exposure to semen, indicating whether intercourse unprotected by condoms took place.

If a biomarker of HIV transmission could be found that would give an early indication of the likely efficacy of a candidate microbicide before thousands of women are enrolled in a Phase III trial, the benefit to the microbicide field, and perhaps others, would be great. Because of this critical potential, work on biomarkers and surrogates of safety and efficacy is a priority action called for by the Microbicide Development Strategy produced under the aegis of the Microbicide Donors' Committee with support from the Bill & Melinda Gates Foundation.

CONRAD has been spearheading the effort to find a biomarker of semen exposure suitable for use in contraceptive and microbicide efficacy trials. In 2004, CONRAD and Ibis Reproductive Health sponsored a meeting funded in part by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Allergy and Infectious Diseases (NIAID), entitled "Evaluation of Markers of Intercourse in Trials of Vaginal Barriers." There are major gaps in knowledge about these markers and work begun at the meeting has been continued by two sub-groups, one devoted to preclinical aspects of markers and one devoted to clinical aspects, under the direction of CONRAD. The clinical group has been especially active since January 2005. Two studies are already underway as a result of its work, and a manuscript was recently submitted for publication by collaborating investigators. The preclinical group has compiled a list of potential new biomarkers of semen, and has outlined the initial experiments needed to characterize and validate them.

CONRAD and the Alliance for Microbicide Development also sponsored a meeting in Reston, Virginia in November 2006 that reviewed the current status of biomarkers, not just of semen exposure but of inflammation and HIV exposure. The meeting served to assess how emerging technologies from other industries might be applied to the microbicide field, and to encourage innovation and collaboration among a broad spectrum of researchers within and beyond that field. Proceedings from the meetings will be published as a supplement in the journal *Sexually Transmitted Diseases*.



Major Activities and Advances in 2006-2007

Contraception

Male hormonal contraceptive effectiveness trial

Partner: World Health Organization (WHO)

The collaboration between WHO, CONRAD and the Consortium for Industrial Collaboration in Contraceptive Research (CICCR) made progress in obtaining the regulatory and ethical agreements required to start a Phase II contraceptive effectiveness trial based on a hormonal method for men. This trial will be conducted in seven countries and enroll approximately 400 couples. Recruitment is expected to begin in mid-2008.

The SILCS diaphragm, a new single-size barrier device

Partner: The Program for Appropriate Technology in Health (PATH)

An Investigational Device Exemption (IDE) was filed with the Food and Drug Administration to prepare for a contraceptive study with a new single-size barrier device, the SILCS diaphragm. Since the SILCS diaphragm will be used with BufferGel™, it has the potential of dual protection, as BufferGel™ is a product in an on-going Phase III trial on HIV prevention. A Phase III contraceptive trial, enrolling 450 couples in six U.S. sites, was initiated in January 2008.

Meloxicam, a non-steroidal, anti-inflammatory agent to be used in emergency contraception

Partner: Hewlett Foundation

Two studies were completed with the non-steroidal, anti-inflammatory agent meloxicam that have suggested it may improve the efficacy of levonorgestrel (LNG) when used for emergency contraception and that it may even be effective for that purpose when used alone. LNG is currently the main product used for emergency contraception and has a limited range of effectiveness (three days after unprotected sex). Meloxicam may expand the window of effectiveness and have fewer side effects. A new study to explore these possibilities was funded by the Hewlett Foundation and initiated in the fall of 2007 in Santiago, Chile.

Cellulose sulfate as a contraceptive

Partner: Polydex Pharmaceuticals

A Phase II trial of 200 couples to test the contraceptive effectiveness of "Ushercell," a gel containing 6% CS was completed. The results showed that Ushercell was contraceptive with a six-month typical-use pregnancy probability of 13.4% and a "perfect-use" rate of 3.9%, which compares well with a recent study of the products currently on the market. Over three-quarters of the women and their partners in the study reported that they would buy Ushercell to prevent pregnancy.

Major Activities and Advances in 2006-2007

Contraception

Non-hormonal approaches to male and female contraception

Partner: Schering AG

Work continues on several promising new targets for non-hormonal approaches to male and female contraception, all at a very early stage of development in animal models. CONRAD/CICCR partnered with Schering AG to co-support two networks of investigators to evaluate targets for contraception, one network for male leads (AMPPA-II) and one network for female leads (Female AMPPA). Although both partners judged the collaboration successful based on the fact that the projects were due to continue, completion of the development activities was constrained by available resources and corporate re-prioritization that occurred when Bayer AG took over Schering AG in early 2006.

Female condoms

Partners: PATH and Medtech Products

CONRAD has continued its pioneer work with female condoms that help lead to the 1993 FDA approved of the only female condom on the U. S. market today, FC Female Condom (formerly Reality® Female Condom), marketed by The Female Health Company. Initial evaluation of two new female condoms – PATH's "Woman's Condom" and Medtech Products' female condom, developed by Dr. A.V.K. Reddy – was completed and larger studies have begun.



Reducing unintended pregnancies among women living with HIV is a powerful but not yet widely used option to reduce mother-to-child transmission of HIV. *World Health Organization*

CONRAD 2006-2007 Contraceptive Research	Description	Status	Collaboration
<p>NEW LONG-ACTING PROGESTIN Formulation and sterilization of levonorgestrel butanoate, which will provide progestational activity for three months after a single injection. It is expected that it may have advantages over DMPA for female contraception and may be better than norethisterone enanthate in combination with an androgen for male contraception. A pharmacokinetic study in animals was completed.</p>	<p>Progestins suppress pituitary hormones and thus prevent ovulation. In the absence of suppression of ovulation, other mechanisms include thickening of cervical mucus and altering the secretion of hormones sufficiently to prevent conception.</p>	<p>A pharmacokinetic study in men and women will be needed.</p>	<p>This is a joint project of NICHD, CONRAD and WHO.</p>
<p>NOVEL MALE LEADS One involves a peptide, occludin, conjugated to a mutant FSH which targets the testis and is designed to elicit the release of premature sperm. Inhibition of critical sperm function is the intent of other activities, in particular those focused on retinoic acid receptor, factors required for release of motile sperm (Eppin), on sperm membrane calcium channels (CatSper), and enzymes required for energy production (GAPDHS). Selective small molecule inhibitors have been identified for several of the validated targets.</p>	<p>These new methods would either disrupt sperm production (in the testis), sperm maturation (in the epididymis), or sperm function (after ejaculation). Interference with sperm motility prevents fertilization.</p>	<p>High throughput screening will be required to optimize inhibitory small molecules. Alternative delivery system of the peptide complex will have to be evaluated.</p>	<p>None</p>
<p>NOVEL FEMALE LEADS Four target molecules have been identified as potential leads for novel female contraceptives. For three targets, inhibitory peptides have been developed and their half-life extended by PEGylation. One target is the GnRH II receptor, which predominates in reproductive tissue. Agonistic and antagonistic peptides have been made and selectivity shown for the GnRH II receptor compared to GnRH I receptor.</p>	<p>These molecules are important for establishment of pregnancy.</p>	<p>Isolation and anti-fertility testing of inhibitory peptides by vaginal application in mice, and then other species.</p>	<p>NICHD synthesis facility is making the GnRH II receptor antagonists.</p>
<p>VAGINAL CONTRACEPTION A Phase II contraceptive effectiveness study with 6% cellulose sulfate (CS) vaginal gel has been completed in the U.S. The results were very satisfactory – as good as or better than nonoxynol-9, but with less vaginal irritation.</p>	<p>A less irritating replacement for nonoxynol-9 as a vaginal spermicide is needed.</p>	<p>A Phase III study would be required by the FDA for registration.</p>	<p>An industrial partner is required to underwrite the costs of the Phase III trial.</p>
<p>DUAL PROTECTION Phase III contraceptive trial about to start with a new single-size diaphragm (SILCS) to be used with a gel that may have dual protective capabilities.</p>	<p>Phase III trial is a six-month contraceptive study in 450 couples randomized to use the device with either BufferGel or nonoxynol-9.</p>	<p>This is the only trial needed for registration and a 510(k) submission for the device. If over-the counter status is to be sought, additional studies would be required.</p>	<p>An industrial partner would be required for manufacturing and marketing the device.</p>
<p>EMERGENCY CONTRACEPTION Pilot studies with meloxicam, a Cox-2 inhibitor available in many countries, have shown that it has the potential to be used either as a stand-alone non-steroidal product or combined with levonorgestrel for emergency contraception. Inhibition of Cox-2 results in inhibition of follicular rupture, but luteal development is normal, thus ensuring normal menstrual cycles.</p>	<p>Emergency contraceptives can be taken after unprotected intercourse to prevent ovulation. There is a need for a non-hormonal alternative to the levonorgestrel pill presently available to reduce side effects.</p>	<p>A dose-finding study funded by the Hewlett Foundation is in progress. Once the optimal dose is selected, a Phase II efficacy study will be needed.</p>	<p>Partners for the Phase II study have yet to be identified.</p>
<p>MALE HORMONAL CONTRACEPTION A Phase IIb study of norethisterone enanthate and testosterone undecanoate given intramuscularly every 8 weeks is being studied as a male hormonal contraceptive. This is a multi-site study in 7 countries. The first volunteers will be enrolled in the summer of 2008.</p>	<p>There are no male contraceptive options other than vasectomy (mostly irreversible) or condoms (not practical for long-term use). This will provide a male hormonal method.</p>	<p>The study will take approximately 3 years to complete. If the results are favorable, a Phase III trial will be required.</p>	<p>This is a joint project of CONRAD and WHO. Bayer Schering Pharma has donated the drugs for the study.</p>

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Of all regions, sub-Saharan Africa is the most devastated by the epidemic. No other region approaches its prevalence or displays such a disproportionate impact on women and girls: 77 percent of all HIV-positive women live in sub-Saharan Africa. *UNIFEM Facts & Figures on HIV/AIDS 2004*



Without healthy women,
there can be no healthy nations.

Financial Summary

Project Activities for 2006-2007

Activity Area	(in \$,000's)
Physical Barriers (Contraception and STD/HIV Prevention)	6,025
Chemical Barriers for Contraception	526
Microbicides	34,157
Male Methods for Contraception	1,685
Non-hormonal, non-barrier methods for female contraception	1,673
Long-acting progestagens	264
AIDS (CDC)	322
Extramural Support Services	1,165
Other	550
Total	46,317

CONRAD Support Funding received during 2006-2007

Funding Source	(in \$,000's)
USAID (Population and Contraception)	6,500
USAID (Microbicides)	28,982
Interagency Agreements (NICHD and CDC)	2,474
Gates Foundation (Contraception)	2,912
Gates Foundation (Microbicides)	11,434
Other Private Foundations	1,620
Other	1,550
Total	55,472

CONRAD exists to facilitate the rapid development of safe, acceptable, affordable products which could provide new methods of contraception and/or prevent the sexual transmission of HIV/AIDS and other infections.



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