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SPECIAL REPORT

Current Contraceptive Research

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In making contraceptive choices, couples balance their sexual lives, their reproductive goals, and each partner's health and safety. The search for a choice that satisfies all three objectives presents significant challenges for women and men throughout the world. Furthermore, what constitutes an ideal or suitable contraceptive method differs not only among individuals but also as individuals enter different life phases: A method that works for a sexually active teenager who has had several partners, for example, may not continue to meet her needs as she becomes a monogamous career woman. Therefore, it is important for women and men to have a wide variety of contraceptive options, which will allow them to maximize the benefits and minimize the risks of contraceptive use as their needs change.

To achieve the family size she desires, a fertile woman today must practice birth control throughout most of her potential reproductive years—as many as 30 of the roughly 36 years between menarche and menopause.[1] The amount of time a woman needs contraception has increased dramatically as women have become sexually active at earlier ages and increasingly have entered the workforce, delayed childbearing and planned smaller families.

Successful prevention of unplanned pregnancies relies not only on access to available marketed products, but also on the products' acceptability and couples' willingness and ability to use them effectively. While many women are motivated to avoid unwanted pregnancy, difficulties in using methods consistently, varying side effects and a wide range of failure rates may create obstacles to contraceptive use. For example, many women find it challenging to take a pill every day, and some find it a nuisance to use a chemical or mechanical barrier method at every act of intercourse. Cost may deter some women from using effective methods: In the United States, insurance coverage does not consistently include contraceptives, and out-of-pocket expenses may amount to $300-500 a year for oral contraceptives or other methods. Women in many developing countries face additional obstacles, including cultural biases against certain methods and limited supplies.

The need for new pregnancy prevention options that improve on currently available

methods also has important public health dimensions: Of the estimated 210 million pregnancies that occur worldwide each year, 40% are unplanned.[2] Furthermore, the HIV epidemic has given rise to growing interest in combining contraception with sexually transmitted infection (STI) prevention.

Although research on and development of novel contraceptives have failed to keep pace with the growing need for a variety of safe, effective and acceptable methods, ongoing investigation holds out the promise of a number of new options. These include chemical and mechanical barrier methods, hormonal methods, male contraception, trans-cervical sterilization and immunocontraceptives.

CHEMICAL BARRIER METHODS

Chemical barriers can be used alone or in combination with a mechanical barrier to provide increased protection against pregnancy or STIs, including HIV, or backup in case of mechanical barrier failure. An ideal product would be female-controlled, with minimal systemic exposure and adverse effects, and would have the ability to coat the vagina, cover the cervix and be retained for an extended period of time. The development of such products is of urgent need and has been the focus of a great deal of research activity for the last decade.

Initially, expectations for existing over-the-counter spermicides containing nonoxynol-9 were great. However, studies showing that nonoxynol-9 products may cause irritation of the cervix and vagina, which may form gateways for increased transmission of HIV, have generated concern about these products.[3] Contrary to the expectation that nonoxynol-9 products might reduce HIV transmission, one study demonstrated that HIV incidence was greater in a high-risk population using nonoxynol-9 than in a comparison population using a placebo.[4] A report released by the World Health Organization (WHO) and CONRAD advises women at high risk of HIV transmission against using nonoxynol-9 spermicides for contraception; furthermore, it concludes that when used alone by women at low risk of HIV transmission, nonoxynol-9 is only moderately effective for pregnancy prevention.[5] However, results from a multicenter trial evaluating the effectiveness of five nonoxynol-9 products are under analysis.

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Many novel compounds that have antifertility and possible antimicrobial effects are currently being developed and tested. However, substantial challenges remain before a new contraceptive microbicide product will be available for distribution. Phase III studies* are planned for the more promising candidates, but they depend on satisfactory completion of safety studies, availability of ample clinical supplies,

recruitment of the required clinical sites and availability of funding from the public sector.

Two contraceptive microbicides, PRO 2000 and cellulose sulfate, are far along in the pipeline. These work by inhibiting sperm function and the attachment of pathogens to target epithelial cells. Preclinical studies of PRO 2000, under development by Indevus (formerly Interneuron) Pharmaceuticals, have shown that it is effective as a contraceptive in rabbits and is active against HIV, herpes simplex virus, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. The gel was found to be well tolerated in phase I trials.[6] Cellulose sulfate, developed by Polydex Pharmaceuticals and the Program for the Topical Prevention of Conception and Disease (TOPCAD), is an antifertility agent that does not destroy cells. (By contrast, nonoxynol-9, which destroys target cells, can also harm the cells that line the vagina and cervix.) Results of a phase I single- and multiple-exposure tolerance study suggested that cellulose sulfate gel is as safe as the marketed nonoxynol-9 product Conceptrol and the inactive control K-Y Jelly; the findings also suggested that the new product may be associated with less genital irritation.[7] A related substance, polystyrene sulfonate, has shown activity as a contraceptive and antimicrobial agent, and appears to produce less genital irritation than a nonoxynol-9 product.[8]

Other products aim to enhance vaginal defense mechanisms. These include BufferGel, ACIDFORM gel, *Lactobacillus crispatus* suppository and genetically modified strains of *Lactobacillus*. BufferGel and ACIDFORM gel, which work by maintaining the natural protective acidity of the vagina, show particular promise as both antifertility and antimicrobial agents, while *Lactobacillus* products have potential primarily as antimicrobial agents. *Lactobacillus crispatus* capsules (manufactured by The Medicine Company) may recolonize the vagina with hydrogen peroxide, producing *Lactobacillus*, which helps keep the vagina free of infection.

BufferGel, developed by ReProtect, achieves its protective effect by acidifying semen. It was found to be effective, safe and well tolerated in 27 U.S. women who used the product once or twice daily for 14 days and underwent colposcopy before and after the trial period.[9] Ninety-eight sexually abstinent and sexually active women in four international sites used the product twice daily for 14 days without any serious adverse events.[10] In a standardized postcoital test for barrier contraceptive evaluation, which analyzes the presence and activity of sperm in the cervical mucus after sexual intercourse, BufferGel also demonstrated effectiveness as a spermicide.[11]

ACIDFORM gel, a product of TOPCAD, maintains the natural protective acidity of the normal vaginal environment even in the presence of alkaline semen. Although it is in early clinical testing, comparative in vitro studies have shown that it has greater acid-buffering capability than BufferGel.[12] The product was reported to be safe in a double-blind, phase I clinical safety trial conducted at the University of Campinas in Brazil.[13]

In addition, Savvy, developed by Biosyn, is a surfactant (similar to a detergent) that disrupts the outer surface of sperm and pathogens. After 14 days of use, fewer women using preparations containing 0.5% and 1.0% Savvy than using nonoxynol-9 experienced irritation;[14] all concentrations of Savvy studied in postcoital testing performed well.[15]

For some couples, the decision to discontinue contraceptive use in order to conceive does not eliminate the need for STI protection. The development of a noncontraceptive microbide would give individuals an option to protect themselves against STIs while attempting conception. The leading noncontraceptive microbicide, under development by the Population Council, is Carraguard, a seaweed extract that inhibits the attachment of the pathogen to target mucosal cells. Carraguard is a large molecule, which appears to coat both the pathogen and the vagina; in vitro and animal studies suggest that it blocks infection with HIV, herpes simplex virus type 2, human papillomavirus and *Neisseria gonorrhoeae*. Data from a randomized, placebo-controlled double-blind safety trial in South Africa and Thailand are currently being analyzed;[16] a phase III trial is planned to begin in 2003.

MECHANICAL BARRIER METHODS

Female-controlled mechanical barrier methods have not been widely used or accepted. (For example, among all women at risk of pregnancy, the proportion who use the diaphragm declined from 5% in 1988 to 2% in 1995.[17]) However, they may have a unique ability to cover and protect the cervix.[18] By reducing exposure to infections such as chlamydia and gonorrhea, and protecting the epithelium of the cervix, these methods may offer some protection against HIV.

Several new mechanical barrier methods are being designed to improve over the standard latex diaphragm, which Margaret Sanger introduced in the United States in 1916. Each has unique features, but they share a number of important elements: Compared with a latex diaphragm, they are easier to insert and remove; they are more comfortable and easier to fit; they are more effective barriers; and they are made from medical-grade silicone, a material that is more durable than latex, is safe for those with latex allergies and is compatible with oil-based lubricants.

Lea's Shield (developed by Yama), intended for use with spermicidal gel, is a vaginal contraceptive device made of silicone with a valve allowing the flow of fluid from the cervix to the vagina and a loop that aids insertion and removal. It is designed to be less-easily dislodged than traditional diaphragms, and a single size should fit most women. The device, which will be available by prescription, received approval from the Food and Drug Administration (FDA) in March 2002. The failure rates (i.e., pregnancy rates associated with method use) used in the labeling, based on data from efficacy trials, are 9% for six months and 15% for 12 months. [19]

The Program for Appropriate Technology in Health (PATH) and a private-sector collaborator, SILCS, have received funding from CONRAD to design an improved contraceptive diaphragm. The new silicone device, called the SILCS intravaginal barrier, is easier to use, more comfortable and more durable than available diaphragms; it has a "one-size-fits-most" design and does not require fitting by a clinician. Users of the device evaluated prototype designs and made recommendations for improving the form, fit and function. A preliminary acceptability trial of a fourth-generation prototype of the device and a phase I study comparing postcoital testing and safety of the SILCS diaphragm and the Ortho All-Flex diaphragm (both used with spermicide) supported the safety, comfort, and ease of insertion, use and removal of the device.[20] Clinical trials to evaluate its effectiveness are in the planning stages.

The FemCap is a new silicone vaginal contraceptive device, somewhat like a cervical cap, that fits over the cervix. Shaped like a sailor's hat and manufactured in three sizes, the device is intended for use with spermicidal gel. Several studies have been conducted, including a phase I postcoital study, a phase II/III contraceptive effectiveness study, and a study of how adding a strap to the device affects difficulty with removal and other aspects of function.[21] The original FemCap (without the strap) had an unadjusted failure rate of 14% in six months of typical use, which may be annualized to 23%. The contraceptive effectiveness of the strapped device has not been directly studied, but is unlikely to be significantly affected by the design modifications. FemCap, Inc., has submitted a premarketing application to the FDA.

The HIV crisis...has sparked renewed interest in the development of contraceptives that will revitalize the search for a variety of new and innovative methods.

The BufferGel cup is a device designed to deliver and distribute BufferGel or another spermicide/microbicide to both the cervical and the vaginal sides of the device. It also protects the cervix with a physical barrier preventing direct contact with the penis and ejaculate. The device is undergoing modification and production before phase I testing can begin.

Despite the benefits of a female condom, only Reality (now trademarked as the FC Female Condom), a product of Female Health Company, has been available since it was approved in 1994. Although original studies showed that the female condom was acceptable, clinicians and users have identified difficult insertion, discomfort, unattractive appearance, slippage problems and high cost as obstacles to use. Second-generation female condom products with novel features are currently in development. The Reddy Female Condom, a latex device being developed by MedTech Products in India, differs from the FC Female Condom in materials as well as design, using a sponge rather than a ring as the internal stabilizing mechanism. Additionally, PATH is developing a nonlatex female condom that it expects to be more comfortable, usable and affordable for a wide range of users; the design improvements will rely on user feedback.

FEMALE HORMONAL METHODS

Oral contraceptives have so dominated the U.S. market since their emergence in the 1960s that many women equate the use of birth control with the use of the pill. Research since the pill's introduction has focused on lowering the dose of estrogen and using different dosages and types of progestins, and the pill is now considered safe and effective. Still, efforts continue to both improve on the pill and develop equally effective hormonal alternatives.

The search for a safe, effective and acceptable estrogen-free oral contraceptive is

ongoing. A product without the side effects of estrogen (including venous thromboembolism) and without the higher failure rate and menstrual abnormalities associated with progestin-only pills would be a major advance. In one study, a daily dose of mifepristone (2 mg or 5 mg) administered for 120 days suppressed ovulation and induced amenorrhea in the majority of women.[22] Future studies should evaluate efficacy and long-term side effects, including the lingering safety issue of the risk of endometrial hyperplasia.

Oral contraceptive regimens that reduce the amount of withdrawal bleeding also have been investigated. A regimen consisting of 84 continuous days of ethinyl estradiol and levonorgestrel followed by a seven-day pill-free interval has been designed to reduce the number of withdrawal bleeds from 13 to four per year. The product (from Barr Laboratories) is named Seasonale, because it results in four 91-day cycles per year, or one cycle for each season. Preliminary efficacy data from a multicenter trial found that both Lo and Ultra Lo Seasonale extended regimens (containing 30 mg and 20 mg of ethinyl estradiol, respectively) are as effective as standard oral contraceptives.[23]

Despite these advances, women may find oral contraceptives inconvenient to use and may not fully comply with their prescribed regimen. In a study comparing self-reported pill-taking with data from an electronic device measuring compliance, 53-59% of women reported not missing pills, but the device recorded much lower proportions (19-33%).[24] One response to these difficulties has been the emergence of new types of hormonal contraceptives that are longer-acting and do not require daily attention. The FDA approved a monthly injectable (Lunelle, a product of Pharmacia) in October 2000, a vaginal ring (Organon's NuvaRing) in October 2001 and a transdermal patch (Ortho Evra, manufactured by Ortho-McNeil Pharmaceutical) in November 2001; all of these devices deliver a combination of estrogen and progesterone.

Progesterone-only implants provide extremely effective long-term, highly reversible contraception in women who are unable or prefer not to comply with an oral regimen. Jadelle, a five-year levonorgestrel-releasing two-rod system, is designed to be easier to both insert and remove than was Norplant, the six-rod system that was sold in the United States from 1991 to 2000. The two-rod system received FDA approval in 1996 and was licensed to Wyeth Ayerst, but it has not been marketed in the United States.

One-rod systems are also in development or on the market outside the United States. Organon Laboratories' Implanon, a three-year, single-rod system that releases the progestin etonorgestrel, has been approved for use in the United Kingdom. Fear of litigation may delay the introduction of new implants to the U.S. market. Implanted pellets that release norethindrone have also been studied. The insertion of four pellets led to anovulation in 92% of women studied.[25]

MALE CONTRACEPTION

Research into contraceptives for men focuses on overcoming the drawbacks of the two currently available male methods: the limited efficacy and compliance problems associated with condoms, and the irreversibility of vasectomy.

Results from two clinical trials testing the effectiveness of the use of androgens (male sex hormones) alone were published in the 1990s. In a proof-of-concept trial

sponsored by WHO and CONRAD, 65% of 271 men who received weekly injections of testosterone enanthate reached azoospermia (i.e., the elimination of sperm from the semen).[26] In a subsequent efficacy trial,[27] no pregnancies were reported among the couples in which the men were azoospermic. Pregnancies were reported among those who were oligospermic (i.e., had reduced sperm counts), for a rate of 8.1 per 100 person-years; as one would expect, the number of pregnancies rose with increasing sperm counts. The success rate was higher in Asian men than in white men. Side effects associated with use of testosterone enanthate (and other androgens) include weight gain, acne and adverse effects on serum lipids. This drug is a short-acting ester, which had to be given at fairly high doses, and was never intended to be marketed as a contraceptive.

More recent research on male hormonal methods has sought to improve sperm suppression and prevent side effects related to androgens. The most studied regimens include androgen-progestin combinations that suppress gonadotropins (pituitary hormones), thereby blocking sperm production. Such combinations have been shown to induce azoospermia and clinically significant oligospermia more quickly than androgens alone. Furthermore, progestins allow the use of less testosterone and thereby reduce androgen-related side effects.

One of the major barriers to the development of a male hormonal contraceptive has been the unfavorable pharmacokinetic profile of the available testosterone preparations, which require frequent administration. The recent development of the long-acting formulation testosterone undecanoate represents a major milestone for male hormonal contraception.[28] Oral desogestrel with testosterone pellets was recently found to lead to azoospermia, but requires daily administration of the progestin and a minor procedure for insertion of pellets.[29]

Gossypol, a derivative of cottonseed oil, has also been explored as a male contraceptive. The contraceptive effect of this substance was discovered accidentally, when animals and men consumed cotton cake in times of scarce food supply. In the 1970s, a trial involving more than 8,000 Chinese men who were given gossypol showed that the drug was well tolerated by most; however up to 10% of users had undesirable side effects, including hypokalemia and irreversibility of the contraceptive effect. [30]

A clinical trial of gossypol acetate involving men seeking vasectomy evaluated its efficacy, acceptability and side effects. Among 134 men, 60% attained spermatogenesis suppression by week 16. Participants who attained suppression entered a second phase at a lower dose; about 90% maintained suppression. Fifty percent of participants failed to reach full reversibility within a year of stopping gossypol, but azoospermia persisted in only 19%.[31]

Possible options for male contraception also include ones modeled on the cancer drug lonidamine, which reduces normal sperm production. In early preclinical and animal studies, several analogs that are equally effective but nontoxic have proven to be reversible, to exert their effects locally within the testes and to have acceptable genotoxicity and toxicology profiles.

Other research programs are pursuing agents that act in the epididymis. Since sperm

mature and acquire fertilizing capacity as they pass the epididymis, research is ongoing to identify epididymal targets that could be inhibited. Investigators have focused on membrane channels, secreted proteins that bind to sperm (some of which appear to be involved with sperm-egg fusion) and epididymis-specific enzymes.

TRANSCERVICAL STERILIZATION

Transcervical sterilization techniques, in which the fallo-pian tubes are approached through the cervix instead of through an abdominal incision, offer several advantages over conventional tubal ligation: They do not require general anesthesia or incisions, and they may therefore increase safety, lower costs and improve access to sterilization.[32]

The Essure pbc (permanent birth control) system, manufactured by Conceptus, is designed to provide minimally invasive transcervical tubal access in a half-hour procedure performed in a hospital or an outpatient setting under local anesthesia. Using a hysteroscope and catheter, a physician inserts a tiny coil mechanism into the vagina, through the cervix and to the proximal portion of each fallopian tube, where the coil is released; the device promotes tissue growth in the fallopian tubes that, over three months, provides tubal occlusion. Training for clinicians includes a one-day course, practice on a simulator and performance of 7-10 supervised procedures.

In the first clinical trial of Essure pbc, bilateral device placement was achieved in 85% of women, no pregnancies occurred in 1,894 woman-months of use and 7% of all women experienced adverse events.[33] The pivotal trial, a prospective, multicenter international study of women seeking sterilization, was reviewed by the FDA, which approved the device in November 2002 with two caveats: Conceptus will be required to follow the more than 600 women in the two trials for five years, and the company will have to conduct a study to document the placement failure rate among newly trained providers of the method and to identify factors associated with placement failure.[34] The device will be available in the United States in 2003.

Quinacrine-induced occlusion of the fallopian tubes is an appealing option for use in developing countries because of its low cost. The method involves transcervical insertion of two doses of quinacrine pellets, one month apart, between days seven and 10 of the menstrual cycle. Controversy over the use of intrauterine quinacrine in more than 30,000 Vietnamese women ensued because of concerns about carcinogenicity, and WHO recommended halting usage.[35] Nevertheless, clinical data supporting its efficacy continued to accumulate. Data from long-term follow-up of women in Chile showed 10-year cumulative pregnancy rates of 3% among women 35 or older at the time of quinacrine insertion and 11% among younger women;[36] by comparison, five-year pregnancy rates in Vietnam were 7% for women 35 or older and 13% for those younger than 35.[37] In accordance with WHO and FDA recommendations, carcinogenicity studies in animals will be completed before additional phase III trials begin.

Preliminary animal studies suggest that the antibiotic erythromycin may be more effective than quinacrine for nonsurgical female sterilization.[38] Another novel transcervical sterilization product in development is the Intratubal Ligation Device (manufactured by BioMedical Engineering Solutions), which causes scarring and

permanent tubal occlusion. In addition, the Adiana system (developed by Adiana) facilitates a two-step method, in which a catheter inserted into the fallopian tube uses electric current to create a superficial lesion and remove surface epithelium, and then an implant is placed into the site of the lesion to occlude the tube.[39]

IMMUNOCONTRACEPTIVES

Antigens that stimulate the immune system to produce antibodies that are capable of interrupting the reproductive process—immunocontraceptives—have been under investigation for a long time. The most promising is a vaccine intended to inhibit the function of human chorionic gonadotropin (hCG), a hormone necessary for the establishment of pregnancy. Several versions of the vaccine have undergone preclinical and clinical studies, but they have been mired in controversy over theoretical safety risks and potential for abuse (i.e., administration without consent).

Phase II efficacy trials of one version of hCG vaccine in sexually active fertile women found that immunization with the vaccine is effective (only one pregnancy occurred in 1,224 cycles) when women's antibody levels reach at least 50 ng per ml, and fertility resumes when levels fall to less than 35 ng per ml; booster injections maintaining therapeutic levels are required approximately every three months. Immunization is well tolerated without disturbance of menstrual cycles.[40]

Concerns that the antibody response to beta-hCG may have the potential to cross-react with and interrupt other hormones produced in the pituitary gland have slowed the progress of anti-hCG clinical research.[41] Work on development of immunocontraceptives has for all intents and purposes come to a halt because of the pharmaceutical industry's lack of interest and objections from women's health care activists.

BRIGHTEST PROSPECTS

The development of methods that provide dual protection against pregnancy and STIs is drastically needed. The disappointing findings with nonoxynol-9, rather than hindering the quest to find a contraceptive microbicide, should drive forward the pursuit of safe and effective products. The front-runners—cellulose sulfate, Savvy, PRO 2000 and BufferGel—are all slated to undergo phase III trials in 2003. Carraguard, a microbicide and not a contraceptive, is also a leading candidate, and a phase III effectiveness trial that will involve 6,000 women in Africa is planned to begin in 2003.

The need for methods to help prevent STIs, including HIV, has led to a renaissance of interest in improved barrier methods. Intravaginal devices and female condoms that are designed with a greater understanding of female anatomy and that users can insert more easily than existing devices may increase the acceptability and popularity of mechanical barrier methods. In addition, the development of new durable, inert materials, such as silicone, that will not weaken, oxidize or acquire an odor over time may allow use of these barriers with a wide range of gels and may facilitate use in the varying climates of developing countries.

Surveys have shown that women want contraceptives that are simpler to use and more suitable to their lives than the currently available choices.[42] In response, private

industry has developed longer-acting, user-friendly delivery systems for combination hormonal methods, and new durations of administering oral contraceptives are being evaluated. The use of oral contraceptives that have noncontraceptive benefits, such as reducing menstrual frequency, is hardly a new concept. Off-label continuous administration of oral contraceptives has been practiced clinically for decades and was studied as early as the 1970s.[43]

However, work on the dedicated extended-use product Seasonale marks the start of a rigorous research process, and the near future will probably bring the study of extended patch and vaginal ring usage. As a follow-up to the emergence of low-dose estrogen oral contraceptives, the development of estrogen-free hormonal methods without the side effects of the current progestin-only methods is being actively pursued. The development of an antiprogesterone product for use as a contraceptive would be a major and novel advance. The first male method to reach the shelves will most likely involve androgen-progestin combinations, which have already reached the stage of clinical testing.

Finally, women's health advocates and potential users have been involved in contraceptive research and development, and support for increasing this involvement is growing. These groups should be represented in all decision-making mechanisms and advisory bodies that guide research, to help reduce controversies that threaten the future of research and to better identify the needs and views of potential users.

OBSTACLES TO RESEARCH AND DEVELOPMENT

The urgency of the HIV crisis has accelerated the development of new contraceptive microbicides and barrier methods, but perhaps at the expense of other novel contraceptive methods. Research interests have focused on the development of new delivery systems and extended dosing of hormonal contraceptives that increase choice and improve compliance, but a truly radically different method has not evolved.

Financial factors, political pressures and legal concerns are among the obstacles that have impeded the research and development of new contraceptive products in the United States.[44] Private funders may be hesitant to back contraceptive research and development, despite market potential, because of the large investment required to develop a successful product. Product development costs for pharmaceutical and biotechnology companies in many cases exceed expected returns. Insofar as contraception is bound up with sexuality, it is subject to the same cultural, moral and religious influences, and therefore has political as well as personal dimensions. The growing threat of lawsuits, even those resulting in favorable outcomes, has imposed substantial costs on the pharmaceutical industry and chilled its involvement in contraceptive research.

Because of these factors, most major pharmaceutical manufacturers in the United States have become reluctant to pursue leads, and this reluctance has largely halted funding for research on contraceptives. In turn, the shrinking pool of economic resources has slowed the debut of novel contraceptive products. The financial burden of contraceptive research and development has shifted to nonprofit organizations that rely on support from donors and the public sector. One hopeful outcome of the HIV crisis is that it has sparked renewed interest in the development of contraceptives that

will revitalize the search for a variety of new and innovative methods.

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*Before a drug is approved for the U.S. market, it goes through preclinical laboratory testing and three phases of clinical trials to assess its safety and efficacy. Phase I and II trials involve no more than a few hundred volunteers, while phase III trials typically involve 1,000-4,000 participants recruited in clinic or hospital settings, who are monitored by health professionals. (Source: Wulf D, Frost J and Darroch JE, *Microbicides: A New Defense Against Sexually Transmitted Diseases*, New York: The Alan Guttmacher Institute, 1999.)