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THOMSON AMERICAN HEALTH CONSULTANTS

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Shortening the pill-free interval: New contraceptives take next step

Shorter interval may decrease incidence of hormone-withdrawal symptoms

Do you remember Enovid, the first oral contraceptive (OC)? Introduced in 1960 by GD Searle in Skokie, IL, the pill was formulated for 21 days of active hormones, followed by seven hormone-free days. During the pill-free interval, the superficial portion of the endometrium was sloughed, producing a withdrawal bleeding episode that simulated menstruation.[1] Since that time, conventional pill packaging has contained three weeks of active pills followed by seven placebo pills to provide the same pattern of predictable, coordinated withdrawal bleeds.[2]

Get ready to see a change in pill formulations. The Food and Drug Administration (FDA) has just approved two oral contraceptives with a 24-day dosing regimen: Loestrin 24 Fe (Warner Chilcott, Rockaway, NJ), which uses 24 days of active hormonal therapy and four days of iron-containing placebo pills, and Yaz (Berlex, Montville, NJ), which uses 24 days of active hormones and four days of placebo pills. At press time, both pills were set for April 2006 product launches.

EXECUTIVE SUMMARY

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- Conventional pill packaging has contained three weeks of active pills followed by seven placebo pills to provide a pattern of predictable, coordinated withdrawal bleeds.
- Shortening the duration of the hormone-free interval may aid in decreasing many of the adverse symptoms that women experience during the seven-day hormone-free interval.

Both pills carry an indication for contraception. Berlex is continuing to work with the FDA for an additional indication for use in treatment of premenstrual dysphoric disorder (PMDD). **(*Contraceptive Technology Update* reported on Yaz's research in the article, "Review options in treatment of PMDD," April 2006, p. 41.)**

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Loestrin 24 Fe consists of 24 pills containing 20 mcg of ethinyl estradiol and 1 mg of norethindrone acetate, with four pills of 75 mg ferrous fumarate. The Yaz formulation contains 24 pills of 20 mcg ethinyl estradiol and 3 mg of drospirenone, with four placebo pills.

Why shorten the interval?

When it comes to effectiveness, the Pill is a highly reliable method. It carries a first-year failure rate of 0.3% when it is used correctly and consistently. However, when it comes to typical use, the failure rate during the first year rises to 8%.[3] Women may miss pills or fail to start a pill pack, thereby allowing follicles to develop. Unintended pregnancies also may occur when women discontinue their OC regimen without initiating another effective contraceptive method.

For women using low-dose OCs, the clearance of estrogen and progestin from circulation could lead to ovulation if a new cycle of OCs is not started, notes a recently published commentary.[4] Reducing the number of hormone-free days should aid in decreasing the incidences of ovulation and pregnancy that occur in typical oral contraceptive use when women fail to begin their pill packs on time. **(Review information on the importance of proper pill-taking; see the *CTU* article, "Improve information on oral contraceptives," January 2001, p. 8.)**

According to research, current low-dose pills provide a lesser degree of ovarian inhibition during a seven-day pill-free interval compared with higher-dose pills.[1] Findings from three studies that examined the feasibility of shortening the pill-free interval show that women in the groups receiving regimens with such reduced intervals exhibited greater ovarian suppression than women who received the standard 21/7 regimen.[5-7] In contrast, another study that looked at extending the hormone-free interval from seven to nine days with two low-dose formulations reported that some women had elevated circulating endogenous progesterone levels, providing evidence of luteal activity.[8]

Ease side effects

Side effects can lead women to discontinue Pill use. In a prospective study, 28% of 1,657 women initiating OC use had stopped taking the Pill by the end of six months. Almost half (46%) of the women who discontinued Pill use cited

side effects as their primary reason. The most frequent side effects included bleeding irregularities (12%), nausea (7%), weight gain (5%), mood changes (5%), breast tenderness (4%), and headaches (4%).[9]

Shortening the duration of the hormone-free interval should aid in decreasing many of the adverse symptoms that women experience during the seven-day hormone-free interval.[4]

Symptoms worse in hormone-free interval

To look at this issue, scientists conducted a study to measure the timing, frequency, and severity of hormone-related symptoms in Pill users. To compare women's experiences during active-pill and hormone-free intervals, investigators recruited women to use daily diaries to record pelvic pain, bleeding, headaches, analgesic use, nausea or vomiting, bloating or swelling, and breast tenderness during the two intervals. Scientists found that almost all the symptoms were significantly worse during the seven-day hormone-free interval than during the 21 days of hormone-containing pills.[10]

Some women are choosing to bypass the pill-free interval altogether with the use of the extended-regimen oral contraceptive Seasonale (Duramed Pharmaceuticals, Pomona, NY). The pill, which uses a 12-week regimen of 84 days of active pills, followed by seven hormone-free days, was approved for marketing in the United States in 2003. This extended regimen causes users to have only four withdrawal bleeding episodes per year.

Extended regimens mean fewer refills

Duramed's parent company, Barr Pharmaceuticals, received an approval letter in 2005 for another extended-regimen contraceptive, Seasonique (levonorgestrel/ethinyl estradiol tablets 0.15 mg/0.03 mg and ethinyl estradiol tablets 0.01 mg.). The company is working with the FDA on product labeling and post-marketing commitments to gain final approval.

A big advantage of Seasonale and Seasonique is that there is no way a clinic or pharmacy can require a person to come back every month for refills, because pills are packaged 91 days at a time, says **Robert Hatcher**, MD, MPH, professor of gynecology and obstetrics at Emory University School of Medicine in Atlanta. This packaging means a maximum of only four visits a year instead of 13 visits, says Hatcher.

There is one pill with a shortened pill-free interval that will not be coming to American pharmacy shelves. Minesse (gestodene 60 mcg/ethinyl estradiol 15 mcg), a pill marketed overseas by American Home Products (AHP) Corp. in Madison, NJ, arrived in 2000 on pharmacy shelves in Austria, Belgium, Denmark, Finland, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, and Spain. Research indicates the OC, with its 24 days of active pills and four days of placebo, is safe and well tolerated, provides good cycle control, and improves premenstrual symptomatology.[11] However, Wyeth-Ayerst Pharmaceuticals, AHP's drug division, does not plan to seek FDA approval for the drug, says Natalie de Vane, company spokeswoman.

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States make push to widen access to EC

While the decision to make emergency contraception (EC) available over the counter remains in a holding pattern at the Food and Drug Administration, advocates are moving on the state level to allow pharmacists to dispense EC without a physician's prescription under certain conditions.

Vermont is poised to become the ninth state to allow pharmacists to dispense EC without physician prescription. Five states (Alaska, Hawaii, Massachusetts, New Hampshire, and Washington) allow pharmacists to distribute EC when acting under a collaborative practice agreement with a physician, and two states (Maine and New Mexico) allow pharmacists to distribute EC in accordance with a state-approved protocol. In California, pharmacists can locate a prescriber to co-sign a collaborative agreement to initiate EC or work under the statewide protocol approved by the state's Board of Pharmacy and Medical Board to furnish EC.

The Vermont Senate passed Bill H.237 on March 3; however, because the bill differed slightly from the one previously passed by the House, it was scheduled to return to the House for another vote, says **Barrie-Hope Silver**, marketing director of Planned Parenthood of Northern New England (PPNNE) in Williston, VT. Passage by the House was expected as of *Contraceptive Technology Update*'s press time. Once signed into legislation, the bill should go into effect July 1.

"PPNNE will be working hard in Vermont to establish and strengthen relationships with pharmacists and work with coalition partners to provide training to interested pharmacists on EC," says Silver. "Once trained, pharmacists will be able to enter into agreements with licensed providers so that the pharmacist can counsel on and dispense EC."

Under the new legislation, the collaborative practice protocol will be developed by rule by the state health department, explains **Beth Tarallo**, PPNNE's public affairs manager for Vermont. The protocol will be the basis of the agreement between a licensed practitioner and a licensed pharmacist, says Tarallo. The protocol will include a standard informed consent form (to be signed by the woman receiving the emergency contraception), the information needed by the pharmacist before dispensing the medicine, referral information, counseling information, and forms and documentation. Prior to initiating practice under a collaborative practice agreement, H.237 also requires that a pharmacist complete an approved training program, says Tarallo.

PPNNE and EC coalition partners will help develop and provide training to pharmacists in Vermont who wish to provide EC under the collaborative practice agreement, Tarallo says. Coalition partners such as the Vermont Network Against Domestic Violence and Sexual Assault in Montpelier will play an important role in training pharmacists to screen and care for victims of sexual assault and abuse, says Tarallo.

Legislation in play

Lawmakers in Colorado, New York, Illinois, Kentucky, and Maryland all have introduced legislation this year on pharmacy access to EC through some form of collaborative agreement with a collaborating medical provider, reports **Nicole Monastersky**, spokeswoman for the Oakland, CA-based Pharmacy Access Partnership, an advocacy organization. Legislators in New Jersey and Vermont also have introduced similar legislation, she notes. (Pharmacy Access

EXECUTIVE SUMMARY

Access to emergency contraception (EC) is growing on the state level. Vermont is poised to become the ninth state to allow pharmacists to dispense EC without physician prescription.

- Five states (Alaska, Hawaii, Massachusetts, New Hampshire, and Washington) allow pharmacists to distribute EC when acting under a collaborative practice agreement with a physician, and two states (Maine and New Mexico) allow pharmacists to distribute EC in accordance with a state-approved protocol. In California, pharmacists can locate a prescriber to co-sign a collaborative agreement to initiate EC or work under a statewide protocol to furnish EC.
- The EC pill Plan B now will be available at Wal-Mart pharmacies. The retailer announced that all of its pharmacies were to begin carrying the drug as of March 20, 2006. The company says it will continue to uphold its conscientious objection policy, which allows any of its pharmacy associates who do not feel comfortable dispensing a prescription to refer customers to another pharmacist or pharmacy.

Partnership launched a dedicated web site, www.GO2EC.org, in September 2003 to keep national audiences informed about EC and pharmacy access on a state-by-state basis. Click on "Legislation" to obtain the latest information on state activity.)

The partnership has made an investment in promoting expanded access to EC at the state and national levels, says Monastersky. Through funding from the Menlo Park, CA-based William and Flora Hewlett Foundation, the partnership has created the States Take Action Toward EC Services (STATES) Re-granting Program to provide direct financial support to stimulate EC efforts at the individual state level.

The program awarded seven proposals out of 24 applications from state-level organizations for focused short-term efforts to increase EC commitment of pharmacy stakeholders. Organizations receiving awards include Planned Parenthood of Delaware in Wilmington, Healthy Mothers Healthy Babies Coalition of Hawaii in Honolulu, American Civil Liberties Union of Illinois in Chicago, Pro-Choice Massachusetts Foundation in Boston, American Civil Liberties Union of Mississippi in Jackson, and Planned Parenthood of Northern New England in Williston, VT. These organizations were chosen because they either clearly identified their potential to effectively leverage momentum achieved by current or past state-level activity, or they demonstrated that they would initiate new engagement among a cross-section of stakeholders in states where little activity has occurred, says Monastersky. **(See an upcoming issue of *CTU* for an update of these agencies' activities following the annual STATES meeting in June 2006.)**

Wal-Mart to carry EC

Good news for your patients who get EC prescriptions filled at off-site pharmacies: Plan B now will be available at Wal-Mart pharmacies. On March 3, the retailer announced that all of its pharmacies will begin carrying the drug, manufactured by Barr Pharmaceuticals in Pomona, NY. The move was scheduled to take place on March 20, according to a company-issued press release.[1]

Wal-Mart, which operates more than 3,700 pharmacies in the United States, was the country's only major pharmacy chain not selling Plan B. According to its press release, the company will continue to uphold its conscientious objection policy, which allows any of its pharmacy associates who do not feel comfortable dispensing a prescription to refer customers to another pharmacist or pharmacy.[1]

RESOURCE

To track Wal-Mart's agreement to stock emergency contraception (EC), EC advocates have developed a "Wal-Mart Action Packet." The packet, designed in conjunction with the fifth anniversary of "Back Up Your Birth Control Day" on March 21, contains a suggested list of questions to ask at a local Wal-Mart pharmacy to determine whether Plan B is stocked at the facility, as well as a tracking form. To download the free packet, visit the Back Up Your Birth Control web site, www.backupyourbirthcontrol. org, and click on "Make sure Wal-Mart keeps its promise."

Stocking Plan B in Wal-Mart pharmacies is a major step in the right direction to improve women's access to contraception — particularly EC in pharmacies, says Monastersky. Wal-Mart pharmacies, particularly those in rural and frontier areas, may be the only pharmacy available for miles around, which had created a huge barrier to women seeking Plan B.

"In general, pharmacies are conveniently located and are often open longer hours than physicians' offices," observes Monastersky. "Offering Plan B in Wal-Mart stores offers increased access for women throughout the country." **(See resource listing, above, for information on advocates' efforts to track EC availability in Wal-Mart pharmacies.)**

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'Quick Start' approach eyed for DMPA and patch

Current package labeling for the contraceptive injection depot medroxyprogesterone acetate (DMPA) (Depo-Provera, Pfizer, New York City) calls for the method to be initiated within the first five days of a woman's menstrual period.[1] Oral contraceptives now are being started throughout the menstrual cycle in an approach known as

EXECUTIVE SUMMARY

Researchers are now looking at a "Quick Start" approach for initiating use of the contraceptive injection depot medroxyprogesterone acetate and the transdermal contraceptive.

- The Quick Start approach is in use for women initiating oral contraceptives. It calls for women to take the first pill while in the clinician's office. Quick Start is aimed at improving method acceptability and use by no longer forcing women to wait for their menstrual periods to begin their chosen method.
- Traditional initiation approaches include the "first-day start," which initiates pill use on the first day of the woman's next period, and the "Sunday start," when pill use begins on the Sunday after the menstrual cycle begins.

"Quick Start," in which women take the first pill while in the clinician's office. Quick Start is aimed at improving method acceptability and use by no longer forcing women to wait for their menstrual periods to begin their chosen method.[2]

Would a similar approach work when it comes to DMPA? Findings from a just-released study indicate that while immediate provision of DMPA did not affect patient satisfaction or continuation, it did reduce unintended pregnancies.[3] In the study, only one pregnancy occurred among the women receiving DMPA immediately (Depo Now approach), whereas 18 pregnancies occurred among those who were provided a bridge method of contraception (pills, patches, or rings) and then offered DMPA after 21 days.[3]

Prescribers once instructed women to take one of two approaches when it came to oral contraceptive use: the "first-day start," which calls for pill use to begin the first day of the woman's next period, or the "Sunday start," when pill use is initiated on the Sunday after the menstrual cycle begins.

Quick Start has gained favor since early research indicated that it improved pill continuation rates.[1,4] **(*Contraceptive Technology Update* reported on early Quick Start research in its article, "Will 'Quick Start' give women jump on pill use?" January 2003, p. 4.)** Quick Start is now listed as the preferred method of pill initiation in *Contraceptive Technology*.[5]

Researchers at the Mailman School of Public Health at Columbia University in New York City have just presented their findings on the immediate administration of DMPA in a cohort of young women ages 14-26.[3] In their study, they compared the immediate administration of DMPA ("Depo Now") to the immediate use of short-term hormonal methods that served as "bridge methods" until later DMPA initiation. They sought to determine whether Depo Now resulted in greater method continuation to DMPA across a six-month period as compared to other Quick Start bridge methods (pills, transdermal patch, or vaginal ring).

According to the researchers, findings support the use of immediate administration of DMPA with little adverse affect. While immediate administration does not appear to affect continuation or satisfaction, unintended pregnancy is substantially diminished during the first six months of DMPA use, the researchers state.

To perform the study, young women ages 14-26 seeking to use DMPA were randomized after meeting eligibility criteria to either the Depo Now group (n = 100) or an alternative Quick Start group (n = 250). Those assigned to the Depo Now group received their first injection of DMPA at the conclusion of their first visit, provided each was medically suitable for hormonal contraception and had a negative urine pregnancy test. Those randomized to the alternative Quick Start group were provided with their choice of pills, patch, or ring. Women were told to return to the clinic in 21 days to repeat the urine pregnancy test; those who were assigned to receive a bridge method then got their first injection of DMPA. Women were followed through two more DMPA cycles.[3]

To date, researchers have complete follow-up data on 231 women (Depo Now, 66; pills, 60; patch, 75; and ring, 30). According to the researchers, bivariate analyses revealed no difference in 21-day return rates between those who initiated DMPA immediately (64%) versus those who were randomized to use a bridge method (pills, 70%; patch, 79%; ring, 87%) to start DMPA. Among those who were randomized to the bridge method, 57% (n = 94) of those received their first DMPA injection, while 11% (17 out of 159) remained on their initial method or switched to a different method. Using an intention-to-treat analytic plan, continuation rates and satisfaction at the second (42% Depo Now, 35% pills, 35% patch, and 23% ring) and third (32% Depo Now, 22% pills, 27% patch, and 13% ring) injection visits were not significantly different between the groups. However, 19 unintended pregnancies did occur during the study period, with only one pregnancy occurring in the Depo Now group.[3]

One advantage of the Depo Now approach is that clinicians can provide same-day contraception to women, says **Vaughn Rickert**, PsyD, professor of clinical population and family health at the Mailman School. However, providers must be sure to complete the necessary prerequisites of checking for pregnancy and providing advance emergency contraception, with a second visit 21-28 days later to recheck for pregnancy.

"Returning to the clinic wasn't a huge barrier for our patients," says Rickert. "It also provided an opportunity to check to see how each patient was doing with Depo."

How about patch use?

Researchers also are looking at a Quick Start approach when it comes to initiating use of the transdermal contraceptive (Ortho Evra, Ortho-McNeil Pharmaceutical, Raritan, NJ). Labeling for the patch calls for either "first-day" or "Sunday start" method initiation.[6]

Investigators at the University of Pittsburgh School of Medicine and Magee Womens Research Institute, both in Pittsburgh, conducted a study in which 60 women were randomized to initiate use of the contraceptive patch using Quick Start or on the first day of their next menses.[7] Researchers used telephone contact at six weeks to ensure that the second cycle had been initiated. A single follow-up visit was scheduled after completion of the third patch cycle.

Continuation rates for Groups 1 and 2 were 97% and 93%, respectively, into the second cycle, and 93% and 90%, respectively, into the third cycle. About half of the subjects planned to continue using the patch after the study.[7] Reasons cited for not continuing with the patch were similar to those usually given for the Pill, including such side effects as breast tenderness and weight gain.[7]

Lead author **Amitasrigowri Murthy**, MD, MPH, director of the Division of Family Planning at Jacobi Medical Center, Bronx, NY, says one advantage of using the Quick Start approach with the patch lies in the ease of the counseling session. She says it is easier to have the patient apply the patch in the office, with a review of the calendar to explain the cycle of patch use.

Researchers found that about one-fourth of the women who discontinued patch use did so because they could not afford to pay for the contraceptive.

"Access to all methods of contraception by all women is still limited simply due to expense," say the researchers. "Those subjects who decided not to use the patch after the study proceeded to choose methods that were significantly less expensive and, unfortunately, possibly less effective."

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Keep spotlight on LGV: New cases reported

The next patient at your STD (sexually transmitted diseases) clinic is a young man with a mucoid/purulent anal discharge and a lymph node enlargement in the groin area. He discloses that he has experienced rectal bleeding and constipation and says he has had unprotected sex with four men in the last three months. What is your next move?

EXECUTIVE SUMMARY

Lymphogranuloma venereum (LGV), a form of *Chlamydia trachomatis* not usually present in the United States and other industrialized countries, is now on the radar screens of public health officials since a 2004 outbreak occurred in the Netherlands.

- Whitman-Walker Clinic in Washington, DC, announced in February 2006 that it had identified four LGV cases. Other U.S. cities also have reported cases of the sexually transmitted disease.
- LGV can infect both sexes, although new cases diagnosed so far have occurred among men having sex with men.

Suspect lymphogranuloma venereum (LGV). Whitman-Walker Clinic in Washington, DC, announced in February 2006 that it had identified four LGV cases. The four cases are believed to be the first documented incidents of LGV in Washington-area men who have sex with men, says **Philippe Chiliade**, MD, the clinic's medical director.

LGV, a form of *Chlamydia trachomatis* not usually present in the United States and other industrialized countries, has been on the radar screens of public health officials since a 2004 outbreak in the Netherlands.[1] LGV can infect both sexes, although new cases diagnosed so far are among men having sex with men. **(*Contraceptive Technology Update* reported on the initial outbreak in the *STD Quarterly* article, "CDC warning: Family planners should be on the lookout for lymphogranuloma venereum," inserted in the March 2005 issue.)**

Focus on cases

When public health officials raised the initial alert about LGV, Whitman-Walker Clinic began looking at how best to identify potential cases of the STD, explains Chiliade. Given the clinic's strong focus on meeting the life needs of the gay, lesbian, bisexual, and transgender community and those living with HIV/AIDS, clinic personnel took immediate steps to increase their awareness of potential cases, he says.

Whitman-Walker clinicians use a nucleic acid amplification test (NAAT) of a rectal swab to help detect LGV in patients who have had unprotected anal intercourse. Because the Food and Drug Administration has not cleared the use of rectal swabs for NAATs, laboratories must apply for a Clinical Laboratory Improvement Amendment waiver to perform rectal NAATs, says Chiliade. **(Editor's note: Investigators at the University of Alabama in Birmingham in collaboration with CDC investigators are conducting a clinical trial to evaluate the performance of three commercial NAATs in detecting *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in pharyngeal and rectal swab specimens. *CTU* will report on their findings in an upcoming issue.)**

If NAAT testing is positive, the clinic sends samples to the CDC for final confirmation of an LGV diagnosis, says Chiliade. The CDC recommends the following treatment approaches:

- The most recommended choice is 100 mg of doxycycline, twice a day for 21 days.[1]
- An alternative is 500 mg of erythromycin, administered orally four times a day for 21 days.[1]
- The patient's sex partners from 30 days prior to the onset of symptoms should be evaluated, and they should receive LGV treatment if they are diagnosed with LGV. If these sex partners do not have any symptoms, the CDC recommends they be treated with 1 g of azithromycin in a single dose or with 100 mg of doxycycline, twice a day for seven days.[1]

Because those infected with LGV may present with no visible symptoms, clinic officials are screening for high-risk behavior (such as unprotected anal intercourse) and performing NAATs, says Chiliade.

RESOURCE

The Centers for Disease Control and Prevention's Division of STD Prevention offers resources for LGV diagnosis and treatment on its web site, www.cdc.gov/std. Click on "Chlamydia" on the division's opening page; then click on "LGV Project" to access the resources, which include versions of a provider information sheet, patient information form, and specimen collection form.

Challenges in diagnosis

Few health departments are testing for LGV, as there are no commercially available LGV tests and laboratories must develop their own, says **John Papp**, PhD, team leader of the Chlamydia Laboratory in the Laboratory, Reference, and Research Branch at the CDC's Division of STD Prevention. Clinicians who suspect LGV can contact their state or local health department, which will consult with the CDC as necessary for testing assistance, says Papp. **(See the resource box, above, for CDC resource information.)**

Health care providers should continue to watch for symptoms of LGV in gay and bisexual men and evaluate and treat patients whenever appropriate, Papp notes. CDC reference testing is meant to confirm cases and is not intended to assist clinicians in management of suspected cases of the disease, Papp explains.

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Spray-on contraceptive moves to next step

Scientists are preparing to take the next step in the search for a spray-on contraceptive, with a Phase II trial scheduled for the second half of 2006.

Acrux, a pharmaceutical company based in Melbourne, Australia, has entered into an agreement with the Population Council, a New York City-based research group, to develop a contraceptive spray containing the council's synthetic progestin, Nestorone. The upcoming Phase II trial will evaluate whether the spray inhibits ovulation, states **Diane Rubino**, Population Council spokeswoman.

Acrux and the Population Council began working together in 2003, using Acrux's Metered Dose Transdermal System (MDTS) technology to deliver Nestorone to the skin. MDTS is a hand-held aerosol drug delivery system. The contraceptive spray, delivered via MDTS, would be painless, easy to use, and convenient, the developing organizations say. **(*Contraceptive Technology Update* reported on the spray formulation in the article, "Spray-on birth control: New application eyed," March 2004, p. 28, and the article, "Clinical trials begin for spray-on contraceptive," February 2005, p. 23.)**

According to **Igor Gonda**, chief executive officer of Acrux, market research has shown that many women will prefer the ease and convenience of this method to swallowing pills, taking injections, or wearing patches.

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- Results of a Phase I trial indicate that once-a-day dosing of contraceptive spray provided sustained delivery of the contraceptive agent. The spray was well tolerated, with no serious adverse events recorded.

"The target feature of Nestorone MDTS is a convenient daily spray onto the arm that is more discreet and less irritating to the skin than a patch, and, we believe, will prove to have a better safety profile than other hormonal contraceptives," states Gonda.

Results of the Phase I, proof-of-concept, pharmacokinetic study were presented at the Washington, DC-based Biotechnology Industry Organization's 2005 Annual International Convention. The study was conducted in six healthy women at the Sydney Centre for Reproductive Health Research in New South Wales, Australia. Findings indicate that once-a-day dosing of the Nestorone Metered Dose Transdermal System contraceptive spray provided sustained delivery of the contraceptive agent. Mean serum concentrations of Nestorone were maintained in the target range expected to be effective for contraception. The spray was well tolerated, with no serious adverse events recorded.[1]

Nestorone falls into the category of 19-nor derivatives of progesterone, which are referred to as "pure" progestational molecules, as they bind almost exclusively to the progesterone receptor without interfering with receptors of other steroids.[1] Nestorone has strong progestational activity and antiovulatory potency, with no androgenic or estrogenic activity in vivo.[1]

The synthetic progestin is being considered for use in several potential contraceptive formulations, including vaginal rings, implants, and transdermal systems.[2]

Scientists performed a multicenter one-year dose-finding trial of contraceptive vaginal rings that utilized Nestorone, evaulating three dose combinations of Nestorone and ethinyl estradiol with respect to effectiveness, safety, and acceptability. Results indicate that the studied formulations, used on a 21-day-in and seven-day-out regimen, provided women safe and effective contraception.[3]

Researchers also are examining the use of a Nestorone ring in emergency contraception. Investigators conducted a Phase I clinical trial of a ring with a 15 mcg ethinyl estradiol/150 mcg Nestorone formulation; results suggest the ring may be used as an emergency contraceptive method.[4]

The Metered Dose Transdermal System involves drug delivery via a spray applied once a day. The patient simply pushes a metering pump, similar to those used for nasal sprays, and sprays the formulation on the skin via a proprietary applicator. The

spray most likely would be applied to the skin of the woman's forearm. The alcoholic component of the formulation, which is a solution of the drug and the enhancer in alcohol, rapidly evaporates, and the drug and enhancer permeate the skin and form a drug reservoir in the skin.

Acrux is evaluating its MDTS technology in other products. It has licensed U.S. rights for two formulations to VIVUS of Mountainview, CA. One prospective formulation, Evamist, is in Phase III development for treatment of menopausal symptoms. Another investigational formulation, testosterone MDTS, is being evaluated for treatment of decreased libido in women. Phase II development has been completed for that formulation, according to the company.

References

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Check advances made in microbicide development

While no microbicide has yet moved from the research pipeline to the pharmacy shelf, progress is going forward on several fronts to develop female-controlled physical and chemical barrier methods to prevent HIV and other sexually transmitted diseases (STDs).

Findings from a new study conducted by infectious disease researchers at the Miriam Hospital and Brown Medical School in Providence, RI, indicate that tenofovir, a drug already given orally to treat HIV, also is safe when applied as a vaginal microbicide gel.[1] Results from the multi-site study suggest that tenofovir, when used in a vaginal gel, produces mild or no side effects in HIV-positive and HIV-negative women.[1]

What is the next step in research? The National Institutes of Health is funding a Phase II study of 200 women in the United States and India to evaluate longer-term safety in a cohort of at-risk women, says **Kenneth Mayer**, MD, professor of medicine and community health at Brown University/Miriam Hospital. If that trial is successful, an efficacy trial will follow, says Mayer.

Tenofovir, a nucleotide reverse-transcriptase inhibitor, is the active ingredient found in the antiretroviral drug Viread made by Gilead Sciences in Foster City, CA. Viread was approved for treatment of HIV infection by the Food and Drug Administration in 2001.

Scientists are interested in tenofovir, a nucleotide analogue, because it is easily activated and has a high barrier to resistance, compared with

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- Scientists are examining the gel in a Phase II study.
- Investigators are conducting a randomized, placebo-controlled Phase III trial in South Africa of a microbicidal gel formulation of Carraguard. A sulfated polymer derived from carrageenan, Carraguard has been found to prevent HIV-infected mononuclear cells from binding to vaginal epithelia.

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- ■ Unintended pregnancy: Where does your state fall in prevention efforts?
- ■ Urinary incontinence: Look at pelvic floor muscle training
- ■ Chances to diagnose unrecognized HIV infections are often missed
- ■ Review new research on condom performance

other reverse-transcriptase inhibitors.[2] A phase I study that looked at vaginal application of tenofovir gel demonstrated that it was well tolerated among sexually active women; pharmacokinetic data indicated minimal product absorption.[3] Results of animal studies in monkeys have demonstrated tenofovir's potential to prevent transmission of simian immunodeficiency virus in female rhesus macaques.[2]

To conduct the currently published study, investigators enrolled 84 women, ages 18-45; 24 of the participants were HIV-positive. All participants used the study product for 14 consecutive days, with research sites located at the Miriam Hospital in Providence, the Hospital of the University of Pennsylvania in Philadelphia, and Harlem Hospital and Bronx-Lebanon Hospital Center, both in New York City. The most common adverse effects reported by women in the study group included itching and increased vaginal discharge.[1]

Scientists also evaluated a subgroup of women in the study to determine whether the active ingredient in tenofovir gel was absorbed into their bloodstream. About half of the women were found to have low tenofovir levels in their plasma at one or more times during the 14-day study. More research is needed to see if absorption of tenofovir into the bloodstream could be beneficial or harmful, scientists note.[1]

Another vaginal gel formulation in research is Carraguard, from the Population Council in New York City. A sulfated polymer derived from carrageenan, Carraguard has been found to prevent HIV-infected mononuclear cells from binding to vaginal epithelia.[4] **(*Contraceptive Technology Update* reported on Carraguard in its article, "What will it take for microbicides to go from research into reality?" July 2005, p. 77.)**

Preliminary data from a Phase I clinical trial found that men who applied Carraguard before sex over three months did not experience significantly more irritation than a control group of men using a placebo.[5] According to the Population Council, early research on female use of Carraguard indicates it does not cause significant irritation of the female reproductive tract and that the gel is generally acceptable for use.

A randomized, placebo-controlled Phase III trial of Carraguard is under way in South Africa, says **Diane Rubino**, Population Council spokeswoman. The trial is being conducted through collaborations with the University of Cape Town in Gugulethu, the Medical University of Southern Africa in Soshanguve, and the Medical Research Council in Isipingo. As of February 2006, 5,343 women had enrolled in the study, reports Rubino. The study is designed to determine the efficacy of Carraguard gel in preventing male-to-female vaginal transmission of HIV when applied prior to vaginal sex, and to evaluate its safety when used for up to two years, states Rubino. *(Editor's note: Look for upcoming coverage of microbicide development following the Microbicides 2006 conference, scheduled for April 23-26 in Cape Town, South Africa. The biannual international conference offers updates on recent microbicide research and provides a forum for the discussion of new developments in microbicide research, including behavioral, clinical, social science, community, basic science, and advocacy issues. See the conference lineup at the event's web site, www.microbicides2006.org.)*

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1. Mayer KH, Maslankowski LA, Gai F, et al. Safety and tolerability of tenofovir vaginal gel in abstinent and sexually active HIV-infected and uninfected women. *AIDS* 2006; 20: 543-551.

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CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the articles, using the provided references for further research, and studying the questions at the end of the issue. Participants should select what they believe to be the correct answers and refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity with the June 2006 issue, you must complete the evaluation form provided and return it in the reply envelope provided in that issue to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

5. Kilmarx P, Wankrairoj M, Achalapong J, et al. Safety of Carraguard use by heterosexual men in a six month clinical trial in Thailand. Presented at the Microbicides 2004 Conference. London; 2004. ■

CE/CME Questions

After reading *Contraceptive Technology Update*, the participant will be able to:

- **Identify** clinical, legal, or scientific issues related to development and provision of contraceptive technology or other reproductive services.
- **Describe** how those issues affect service delivery and the benefits or problems created in patient care in the participant's practice area.
- **Integrate** practical solutions to problems and information into daily practices, according to advice from nationally recognized family planning experts.

17. What is the progestin in the oral contraceptive Loestrin 24 Fe?
A. Desogestrel
B. Gestodene
C. Levonorgestrel
D. Norethindrone acetate

18. What is the "Quick Start" approach to initiating oral contraceptives?
A. Pill use begins on the first day of the woman's next period.
B. Pill use begins on the first day following the office examination.
C. Pill use begins on the first day of the next week following the office examination.
D. Pill use begins on the same day as the initial office examination.

19. Which of the following is NOT a common symptom of lymphogranuloma venereum?
A. Mucoid/purulent anal discharge
B. Cheesy white discharge
C. Lymph node enlargement in the groin area
D. Constipation

20. Which is the correct microbicidal action category for tenofovir?
A. Broad entry/fusion inhibitor
B. CCR5 inhibitor
C. Nucleotide reverse-transcriptase inhibitor
D. Viral envelope disruption

Answers: 17. D; 18. D; 19. B; 20. C.

Contraceptive Technology Update *is endorsed by the National Association of Nurse Practitioners in Women's Health and the Association of Reproductive Health Professionals as a vital information source for health care professionals.*