IN THIS ISSUE

This special edition of the Council's quarterly research newsletter gathers from past issues articles describing work related to HIV/AIDS/STIs.

Population BRIEFS

Reports on Population Council Research

Spring 2002 Special Edition

STI PREVENTION

Toward the Development of a Microbicide

The spread of AIDS and other sexually transmitted diseases (STDs) has created an urgent need for products that women can use to protect themselves from these infections. Developing one such product—called a microbicide—is the goal of research in the laboratory of David Phillips, a virologist at the Population Council's Center for Biomedical Research. Phillips's scientific team has been working since 1989 to understand the basic biology of HIV infection and to test compounds that could prevent transmission of HIV and other STD pathogens. Research on both fronts has yielded significant results in recent years, increasing the prospects that women will one day have access to a vaginally applied product that guards against STD infection—either in contraceptive or noncontraceptive form.

Devising a product that is useful to women in developing countries is a priority for Council researchers. To this end, Phillips collaborates with Council colleague Christopher Elias in the Programs Division to engage a group of women's health advocates in the process of microbicide development. Feedback from this group is helping to steer development toward products that meet the needs and accommodate the preferences of women in places where these products are most needed.

From basic to applied research

"Microbicide" is actually a misnomer for the most promising compounds under investigation in Phillips's lab. These substances do not kill microbes; rather, they prevent them from adhering to the epithelial cells that form the outer layer of the reproductive tract.

The decision to test compounds that work in this way was informed by basic research findings in the lab. Prior to this research, scientists presumed that HIV infects the body by entering the bloodstream as "free virus" (independent of a host cell). "Strategies to prevent infection, such as proposed AIDS vaccines, have been based on this assumption," Phillips says.

Most infectious microorganisms enter the body through the intact epithelium of the respiratory, digestive, urinary, and reproductive tracts. Scientists assumed that HIV could not enter this way because epithelial cells lack receptors for the virus. Instead, they hypothesized, HIV must infect the reproductive tract by entering through lesions in the epithelium.

Phillips's research team challenged this assumption by showing that HIV can infect intact epithelial cells *in vitro* (in the test tube). HIV appears to enter the epithelium Trojan-Horse-style—hidden within cells of the immune system. Carried in semen or vaginal secretions, the HIV-infected cells adhere to the reproductive tract epithelium of the sexual partner, then secrete virus onto it.

This finding suggests that transmission of HIV to women through sexual intercourse might be thwarted by coating the female reproductive tract with a substance that inhibits HIV-infected cells from adhering to the epithelium. To be a viable candidate for product development, the substance would not only have to be effective, but also safe,

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More Data Needed Before Male Circumcision Is Advocated

A growing body of research shows that uncircumcised men in certain parts of Africa are twice as likely as circumcised men to be HIV infected. This finding suggests that male circumcision may offer a measure of protection against HIV infection, and public health experts have begun to debate the possibility of encouraging male circumcision as an anti-HIV intervention. To explore this issue, the Population Council's Horizons Program organized a two-day meeting of scientists from around the world. The participants identified several cultural, medical, and ethical issues that should be explored before the procedure is recommended as an intervention.

Many unknowns

Little is known about the biological mechanism by which males are infected with sexually transmitted HIV or about the role of the foreskin in relation to such infection. The foreskin has a high density of Langerhans' cells, believed to be involved in certain immune responses, a circumstance that may play a part in initial HIV infection. "Other key issues that have not been resolved include the role that the anatomy of the foreskin and penile hygiene may play in HIV transmission," says Johannes van Dam, deputy director of the Horizons Program. The foreskin, he explains, may provide an environment for the survival of bacterial and viral matter and may be susceptible to tears, scratches, and abrasions, thus increasing the likelihood of contracting HIV.

Van Dam and his colleague Marie-Christine Anastasi collaborated on a publication summarizing a number of knowledge gaps and research recommendations discussed at the meeting. The publication can be downloaded from the Council's Web site at http://www.popcouncil.org/horizons/reports/circumcision/default.html.

There has been little research, as well, into the feasibility and acceptability of male circumcision as a public health intervention. For example, most circumcisions in Africa today are performed by traditional practitioners, who may not operate under sterile conditions. Some methods of circumcision may place boys and men at risk for infection, sepsis, hemorrhage, partial penile amputation, or even death. Certain practices, such as using the same knife for each man during a circumcision ceremony, may increase the risk of transmitting HIV through blood-to-blood contamination.

The cost-effectiveness of such an intervention in developing countries also cannot be overlooked. "We must always strategically prioritize to achieve maximum health benefits for the limited resources available for HIV prevention…we should not rush to put these meager resources into an unproven strategy like male circumcision just because it's new," explains conference participant Francis Ndowa of the World Health Organization.

Men have referred to circumcision as the "invisible condom."

Importance of age

Furthermore, not enough is known about the relationship between age at circumcision and risk of HIV infection. While it is likely that circumcision offers a similar level of protection to HIV-negative men regardless of the age at which it is performed, older men may be more likely to be infected with HIV than are younger men. Circumcision may be most protective against HIV acquisition when it is done before or soon after the onset of sexual activity.

Finally, while male circumcision may benefit men, questions remain as to whether the practice would make women more or less vulnerable to HIV infection. For instance, a reduction in HIV infection in men will over time reduce the exposure of women to sexually transmitted HIV infection. If men believe they are protected from HIV infection by circumcision, however, women's efforts to negotiate condom use may suffer. Van Dam and Anastasi report that men have referred to circumcision as the "invisible condom."

Further research

These questions and others will not be answered without further research. Participants at the conference suggested several necessary avenues of investigation that public health scientists should explore before recommending circumcision as a blanket intervention to combat HIV infection. "We need to move interventions from the domain of myth, culture, and religion to the science of public health," notes meeting participant Robert Bailey of the University of Illinois at Chicago.

Researchers should examine the transmissibility of HIV infection to women by circumcised and uncircumcised men; analyze the role of possible confounding factors, such as religion; conduct randomized controlled trials of a male circumcision intervention to examine its efficacy in preventing HIV infection; conduct descriptive studies of attitudes and beliefs regarding male circumcision as an acceptable HIV intervention in currently non-circumcising populations; test mechanisms for implementing voluntary, safe, and effective male circumcision interventions; and develop and field test a rapid-assessment tool to evaluate the feasibility and cost of introducing male circumcision. ■ September 2000

SOURCE

van Dam, Johannes and Marie-Christine Anastasi. 2000. "Male circumcision and HIV prevention: Directions for future research." Horizons program report. Washington, DC: Population Council.

OUTSIDE FUNDING

United States Agency for International Development

Investigating Links Between HIV and Partner Violence

Encouraging clients to inform partners of their test results is an important component of HIV voluntary counseling and testing programs. Yet many clients do not disclose test results to their partners. Studies have found that many women fear their partners will react violently and that indeed HIV-infected women are at increased risk for partner violence. Researchers with Muhimbili University College of Health Sciences and the Population Council's Horizons program explored the links between HIV infection, the disclosure of test results, and partner violence among women attending the Muhimbili Health Information Center, a voluntary counseling and testing clinic in Dar es Salaam, Tanzania.

The researchers studying HIV and partner violence first collected qualitative data from 62 people—women, men, and couples—who were clients at the Muhimbili Health Information Center. In the second phase, researchers followed 245 women and interviewed them three months after enrollment and HIV testing. Nearly a third of the sample were HIV-positive, almost half were married, and 50 percent were between the ages of 18 and 29 years.

The study, conducted in 1999, found that 64 percent of HIV-positive women shared test results with a partner within three months of testing, compared with nearly 80 percent of HIV-negative women. Overall, the major reason for nondisclosure is fear of their partner's reaction, principally fear of abuse or abandonment.

The Horizons Program

The Population Council's Horizons program employs operations research to understand the types of interventions that work to prevent HIV transmission, to deliver care and support, and to mitigate the effects of AIDS. USAID-funded Horizons research is conducted in collaboration with the International Center for Research on Women, the International HIV/AIDS Alliance, the Program for Appropriate Technology in Health, Tulane University, Johns Hopkins University, and Family Health International.

The problem of partner violence

Partner violence is a serious problem among many of the clinic's female clients. More than one-fourth of women interviewed agreed with the statement, "Violence is a major problem in my life." Study participants, both male and female, described violence as a way to "correct" or "educate" women, and said that violence that does not leave a physical mark on a woman is justifiable.

When asked about lifetime violence by an intimate partner, 39 percent of women had had at least one physically abusive partner and 17 percent had had at least one sexually abusive partner. Physical violence by a current partner was also commonly reported. Nearly a third of women had experienced at least one physically violent episode perpetrated by a current partner in the three-month period prior to testing.

A small proportion of women who informed their partners of their test results reported a negative reaction. Most women said that partners showed support and understanding when told of the test results. However, the proportion of women who reported this positive reaction was significantly greater among HIV-negative women than among HIV-positive women (82 percent vs. 49 percent).

Twelve women reported one or more negative responses by a partner after disclosing their test results. These included being physically assaulted (one HIV-negative woman and two HIV-positive women) and being told to leave the house or being abandoned (one HIV-negative woman and three HIV-positive women). Given the amount of violence experienced by women in this study, there is considerable and justifiable fear of a partner's violent reaction. The study revealed little evidence, however, that the act of disclosing HIV test results frequently leads to physical abuse and abandonment.

Being an HIV-positive woman is strongly associated with experiencing partner violence. Young HIV-positive women (18–29 years) were ten times more likely than young HIV-negative women to report partner violence, controlling for socio-demographic variables. As compelling as this evidence is, the study was constrained by the limitations of cross-sectional surveys and cannot thoroughly illuminate the link between partner violence and HIV infection.

Program and policy recommendations

The researchers offered several recommendations based on their findings. Communication between couples about HIV/AIDS and HIV testing should be encouraged when promoting voluntary counseling and testing. Moreover, "counselors need to be trained in how to ask sensitive questions about violence and to use this information to foster but not force disclosure among clients," says Suzanne Maman of Johns Hopkins University, a principal investigator for the study. Counselors must also be made aware of existing services to help women living in violent relationships so that they can make appropriate referrals when necessary.

Policymakers should encourage community-based efforts to address issues related to violence within sexual relationships. Implementing programs that focus on conflict resolution is crucial.

Finally, investigators should conduct further research on HIV and violence; the findings from this study highlight many gaps in knowledge on this topic. Researchers should assess the feasibility of engaging people chosen by women—such as counselors, friends, or religious leaders—to help women disclose their test results. Social scientists need to identify the links between partner violence and HIV infection. And investigators should evaluate community-based interventions that attempt to change harmful attitudes about sexuality and violence. ■ June 2001

SOURCE

Maman, Suzanne, Jessie Mbwambo, Margaret Hogan, Gad Kilonzo, Michael Sweat, and Ellen Weiss. 2001. "HIV and partner violence: Implications for HIV voluntary counseling and testing programs in Dar es Salaam, Tanzania," Horizons project report. Washington, DC: Population Council.

OUTSIDE FUNDING

United States Agency for International Development

Role of Dendritic Cells in HIV Infection Clarified

The immune system is made up of several kinds of cells that function in concert to provide humans and animals with protection against pathogens. Often, this system works flawlessly, quashing infections before they can kill their host. Sometimes, however, the system fails and infection prevails. This is what happens, for example, when people are infected with the human immunodeficiency virus (HIV), which causes AIDS.

Scientists have been investigating the immune system for decades, yet there is still much that remains unknown about its function. One of the least-understood members of the immune system family is the dendritic cell. Accounting for only about one percent of all immune system cells, dendritic cells, one type of leukocyte, are nevertheless vital to both the initiation and control of immune responses.

Immunologist Melissa Pope, who recently joined the Population Council's Center for Biomedical Research, has studied the action of dendritic cells during HIV infection for the past decade. In parallel with human studies, Pope uses rhesus macaques and the simian immunodeficiency virus (SIV) to model human HIV infection. Her findings have contributed to one of the widely accepted theories for the mechanism of sexual transmission of HIV. Positioned within the mucosa, dendritic cells are one of the first white blood cells that meet HIV following sexual or perinatal transmission and may be pivotal for the onset and spread of infection. Ultimately, Pope's work may identify ways to block the mucosal transmission of HIV with microbicidal formulations. This work may also provide clues in the search for an HIV vaccine.

Antigen-presenting cells

In their immature stage, dendritic cells engulf pathogens and degrade them into protein fragments. As they migrate via the afferent lymphatic system to the draining lymph tissues, immature dendritic cells evolve into mature dendritic cells. They then display the protein fragments from the degraded pathogens on their cell membranes. Other immune system cells, B-cells and T-cells, recognize proteins and protein fragments, also known as antigens, and launch a potent antigen-specific immune response. Thus, dendritic cells are known as "antigen-presenting cells."

This chain of events does not appear to occur successfully when dendritic cells encounter HIV, however. When dendritic cells come across HIV and subsequently interact with T-cells, the encounter, rather than triggering a powerful immune response that should clear infection, spurs a great increase in viral replication. Pope's lab is conducting parallel *in vitro* studies involving immature and mature dendritic cell subsets and SIV. With these studies, Pope and her team aim to understand the early events of dendritic cell–HIV interactions, with the goal of optimizing the presentation of HIV antigens on the surfaces of dendritic cells in order to activate T- and B-cell responses instead of facilitating virus spread.

Dendritic cells can promote HIV replication and growth.

Virus localization

These experiments have revealed that the virus becomes localized in different areas of dendritic cells depending on the cells' maturity level. Pope and her colleagues noted a peripheral localization of the virus in immature dendritic cells, with small vacuoles containing one or two intact viral particles near the cell membrane. In mature dendritic cells they noted an intense intracellular localization of numerous intact viral particles in large vacuoles near the nucleus.

Pope and her team are investigating the implications of these two distinct localizations. They believe immature and mature dendritic cells may use different mechanisms to entrap viral particles. Understanding these uptake mechanisms is the first step in devising ways to block them, says Pope.

Their experiments further showed that dendritic cells do indeed process some of the virus and display antigens on their membranes to be presented to T-cells. Pope and her associates will now attempt to determine ways to boost this antigen presentation and, along with it, subsequent immune activation.

In addition to providing clues about virus uptake in dendritic cells for immune stimulation, these experiments may give insight to the ensuing spread of virus from dendritic cells to T-cells. Pope is investigating whether viral particles remain intact, not infecting the dendritic cells they occupy, until they get transmitted to T-cells, or whether dendritic cells eventually do become infected and spread newly formed virus to T-cells.

"We still have a lot to learn about the interactions between HIV, dendritic cells, and other immune cells," says Pope. "But this basic research, mapping out these microscopic cellular activities, lays the groundwork for the development of microbicides and vaccines that may one day save people's lives." ■

December 2001

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OUTSIDE FUNDING

The Elizabeth Glaser Pediatric AIDS Foundation, the National Institutes of Health, and the Rockefeller Foundation

Nonoxynol-9 Rapidly Exfoliates Rectal Epithelium

New findings, deemed "sobering" by the Population Council scientists who conducted the research, suggest that products containing the spermicide nonoxynol-9 may increase the risk of HIV infection when used during rectal intercourse. David M. Phillips, of the Council's Center for Biomedical Research, and his colleagues found that nonoxynol-9 caused the rapid exfoliation of epithelium when applied rectally.

Surveys in the United States have shown that 41 percent of men who have sex with men try to use products containing nonoxynol-9 as lubricants during rectal sex. This practice stems in part from a belief that such products may act as microbicides, protecting against infection with HIV. In addition to its ability to kill sperm, nonoxynol-9 (N-9) has been shown to inactivate viruses, including HIV, *in vitro* and can protect Rhesus macaques from vaginal infection with SIV, a simian virus related to HIV. The results of a clinical trial reported in 2000, however, showed that the use of products containing N-9 increased the likelihood of HIV infection in women. Other studies, done by Phillips and his colleagues, showed that N-9 caused mouse rectal epithelial cells to slough off and made mice highly susceptible to infection with herpes simplex virus-2, a virus structurally similar to HIV.

Testing N-9 in humans

After obtaining these results in mouse studies, Phillips and his team set out to determine the effect of N-9 on human rectal epithelium. The scientists compared the effects of two over-the-counter gels containing N-9—K-Y® Plus and ForPlay®—and two gels that do not contain N-9—methyl cellulose and Carraguard™, the Population Council's leading microbicide candidate. Carraguard is made from carrageenan. (In 2000, Council researchers began conducting expanded safety and acceptability trials of Carraguard among women in South Africa and Thailand. The placebo used for comparison in these trials is methyl cellulose.)

Phillips and his colleagues examined rectal saline lavage specimens taken from four randomly chosen study participants: three men and one woman. Each participant was given a kit that contained the four test products in unmarked containers. Before applying any of the products, the study participants took a baseline lavage specimen, rinsing the rectum with saline and depositing the specimen in a collection vial containing fixative. Next, the participants applied the first formulation rectally and retained it for 15 minutes, then performed a lavage and collected the specimen.

> *"We caution against the use of N-9-containing products during rectal intercourse."*

Eight to ten hours later, participants collected another lavage specimen. Each product was tested in this way, with participants allowing at least 72 hours between experiments. A total of 36 specimens were collected.

The four specimens collected 15 minutes after the application of K-Y Plus and two of the specimens collected 15 minutes after the application of ForPlay held contents the scientists termed "dramatically different" from the other specimens. These specimens contained hundreds of convoluted sheets of epithelial cells, large enough to be seen with the naked eye. Each sheet typically contained hundreds of cells. The specimens collected after the application of K-Y Plus, which is 2 percent N-9, contained far more cells than the specimens collected after the application of ForPlay, which is 1 percent N-9.

When the scientists examined these six specimens microscopically, they found that each sheet contained columnar and goblet cells, varieties of cells typical of rectal epithelial morphology. In contrast, the other specimens were composed primarily of unidentifiable amorphous material, plant cell walls, bacteria, and an occasional epithelial cell.

"Removal of the rectal epithelium may enhance HIV infection because the primary target cells of HIV, lymphocytes and macrophages, are located in the lamina propria immediately below the gut epithelium," Phillips concluded. "We therefore caution against the use of N-9-containing products during rectal intercourse."

These findings challenge the conclusions of other scientists who recently found that Advantage 24®, a product containing N-9 at 3.5 percent, was not associated with rectal epithelial disruption. The researchers came to this conclusion on the basis of rectal tissue biopsies taken 12 hours after the application of Advantage 24. Phillips and his colleagues argue that the gastrointestinal epithelium rapidly repairs itself. Thus, biopsies taken 12 hours after N-9 application would not accurately show how the chemical damages rectal epithelium. This contention is supported both by the team's previous mouse studies, which showed that mouse rectal epithelium recovered from N-9-induced damage in one hour, and by the current research, which showed epithelial damage 15 minutes after N-9 application, but no sloughing of epithelium eight to ten hours after N-9 application.

Still, Phillips acknowledges that more research is needed. "We're working to prove more convincingly—with larger sample sizes—that use of N-9 during anal sex is risky. We'd also like to determine more precisely the length of time needed for rectal epithelial repair. One paper won't do it." ■ March 2001

SOURCE

Phillips, David M., Clark L. Taylor, Vanaja R. Zacharopoulos, and Robin A. Maguire. 2000. "Nonoxynol-9 causes rapid exfoliation of sheets of rectal epithelium," *Contraception* 62(3): 149–154.

OUTSIDE FUNDING

The Bill and Melinda Gates Foundation, the Andrew W. Mellon Foundation, and the Rockefeller Foundation

Tools and Training Strengthen African AIDS Groups

In sub-Saharan Africa, AIDS has stricken some 21 million adults and children, according to recent estimates. In the early 1990s, many grassroots organizations sprang up in response to the devastation. Population Council researchers Ann Leonard and Esther Muia undertook four collaborative interventions to further strengthen such groups. The efforts demonstrated that providing simple, carefully selected forms of technical assistance can greatly improve the ability of grassroots organizations to achieve their goals.

"These results give valuable insight into how the international community can support grassroots groups—beyond direct financial aid. Modest investments of time and expertise, made in collaboration with the groups, can yield generous returns," says Leonard.

The effort began in 1993 when the Population Council and Glaxo Wellcome established a project on Community-based AIDS Prevention and Care in Africa: Building on Local Initiatives. The first phase entailed a survey of 65 community-based organizations in Kenya, Tanzania, Uganda, Zambia, and Zimbabwe and documentation of eight particularly successful groups as case studies.

"We highlighted the elements essential to good programs for other people who are interested in making these types of efforts, so that they do not have to reinvent the wheel," Leonard says.

"When we began the intervention phase, we wanted to do research that would also immediately benefit the groups themselves," she continues. In collaboration with four of the eight groups and with the help of local colleagues, the researchers tailored projects that would also address problems typical of many growing and successful volunteer groups.

A notebook, a plan

In Uganda, the National AIDS Control Program's Community Counseling Aides (CCA) Project deploys trained volunteers to conduct AIDS education and provide basic nursing care. When the Council intervention began, the goal of having local communities administer and support this program was hampered by a lack of information about the program's performance.

Researchers developed simple yet effective monitoring tools in a report format in which CCAs record their activities and complete monthly worksheets; their supervisors then summarize the results for review by local supporting agencies. After the intervention, the local government in one district began to include the CCAs in discussions on planning the allocation of funds, and the health establishment gained greater respect for the work of the volunteers.

KIWAKKUKI, a women's group in Moshi, Tanzania, provides AIDS education and care for people affected by AIDS. At the time the intervention began, the group had grown so rapidly that its ad hoc structure could no longer cope with the range and scale of activities. Here, creating an organizational structure and management system to improve services was the intervention goal.

Group members and others concerned in the group's mission analyzed the organization's problems and developed solutions. A new organizational structure was put into place and evaluated after one year. Creation of committees reduced overlapping efforts and evened out the burden of responsibility, a branch system increased the group's membership and outreach, and a fundraising committee broadened the base of support.

Giving new skills

In Ndola, Zambia, the INDENI Petroleum Refinery's HIV/AIDS Committee conducts educational activities, provides condoms and medical care, and addresses the needs of employees' families. But because committee staff nevertheless felt they were not sufficiently changing people's attitudes and behavior, the intervention concentrated on developing and testing culturally appropriate counseling methods.

Participation in a series of workshops, exercises, and field work experiences resulted in participants feeling more skillful and more committed. The effectiveness of the approach, as reflected within the community, will be assessed through such measures as focus group discussions, clinic and field work notes, and other indices.

In Lusaka, Zambia, the women of the KWASHA MUKWENU care for children orphaned by AIDS. When they joined the Council intervention, the women were interested in expanding the income-generating skills of older orphans.

The skills orphans most wanted to learn were carpentry and tailoring, so intervention staff organized classes. Participants in the tailoring workshop completed the curriculum ahead of schedule and, with their first earnings, repaired the KWASHA MUKWENU sewing machines and purchased fabric. They now hope to set up a sewing cooperative. The carpentry workshop, which is still underway, entails lessons, an apprenticeship, and an opportunity to be tested for a professional certificate.

In their report on the intervention, Leonard and Muia note that the sewing workshop imparted more than tailoring skills: "Initially quiet, shy, and soft-spoken girls have now become budding entrepreneurs, full of determination to succeed."

And in reflecting on the project overall, Leonard says, "As terrible as AIDS is, the response of these people is truly inspiring." Muia echoes the thought: "We are building on the inherent courage and creativity of the African people. Community-based responses inspire hope, rather than helplessness, as a response to the AIDS crisis." ■ September 1998

SOURCE

Leonard, Ann and Esther Muia. 1998. *Community-Based AIDS Prevention and Care in Africa, Building on Local Initiatives: Results of Four Action-Research Interventions in East and Southern Africa.* New York: Population Council. (In English and French.)

OUTSIDE FUNDING

Glaxo Wellcome, Swedish International Development Cooperation Agency

Syndromic Method Poor at Detecting STIs in Women

Since the early 1990s there has been evidence that some reproductive tract infections (RTIs) enhance the transmission of HIV, the virus that causes AIDS. Because of this finding, the Programme of Action developed at the 1994 International Conference on Population and Development in Cairo endorsed the integration of the diagnosis and treatment of these conditions into maternal and child health/family planning programs. To encourage this integration, public health institutions have developed screening tools intended to assist in the diagnosis and management of various RTIs, including such sexually transmitted infections (STIs) as gonorrhea and chlamydia. (These STIs are 50 percent to 300 percent more prevalent among women than among men.)

These tools were created because standard laboratory tests to identify some STIs are expensive and require equipment that is generally unavailable to clinics in developing countries. The primary screening approach developed, syndromic management, diagnoses infection based on the presence of vaginal discharge, lower abdominal pain, or other symptoms, signs, or risk factors, rather than on laboratory tests. Clinics began using this method before it had been adequately evaluated.

Three recent studies conducted by Population Council researchers and their colleagues find that the syndromic approach is not an effective strategy for diagnosing or managing gonorrhea, chlamydia, and other RTIs among women. One study was a meta-analysis, which reviewed and evaluated 32 peer-reviewed, published studies of the syndromic approach for detecting chlamydia and gonorrhea. The other two studies assessed the efficacy of the method when used to diagnose and manage chlamydia, gonorrhea, trichomoniasis, candidiasis, and bacterial vaginosis. One study took place at the Nakuru Municipal Council family planning and antenatal care clinics in Kenya. The other was designed to obtain information that would enable the Zimbabwe National Family Planning Council to develop the most appropriate and cost-effective approach to managing RTIs in its clinics.

Low sensitivity, high false positive rate

All three studies found that the syndromic management approach has low sensitivity (correctly identifying women who have the condition), moderate specificity (correctly identifying women who are not infected), and results in high false-positive rates. The meta-analysis, for example, revealed that the average sensitivity of the method in groups of women with a moderate prevalence of gonorrhea and chlamydia (an average of 7 percent) is about 35 percent. Specificity in that situation is roughly 75 percent, but the false-positive rate is approximately 90 percent. The study in Zimbabwe arrived at similar conclusions, while the Kenya study indicated that the approach correctly identified only about 5 percent of family planning clients with RTIs and 16 percent of women with RTIs who attend antenatal clinics.

The syndromic approach is not an effective strategy for diagnosing or managing gonorrhea or chlamydia in women.

These results show that clinicians do not identify the majority of women with infections when they use the syndromic approach and that they needlessly expose many uninfected women to treatment and the stigma associated with infection. One reason for the failure of this method is the fact that a large number of women with RTIs have no clinical signs or symptoms suggestive of an infection.

"The syndromic approach to diagnosing cervical STIs in women is not helpful and is potentially harmful because it reduces the time in which physicians can be doing something else that is known to be beneficial for clients," emphasizes Beverly Winikoff, director of the Council's Reproductive Health Program and an author of the meta-analysis study. The authors of the meta-analysis also note that these findings probably overestimate the validity of the syndromic approach because, in everyday use, physicians are unlikely to be as thorough in their application of the method as they were during the various studies.

Recommendations

These findings highlight the importance of developing simple, inexpensive, and valid field diagnostics, particularly for identifying and treating women with gonorrhea and chlamydia. The researchers acknowledge that there is no simple, inexpensive way to effectively diagnose women with gonorrhea and chlamydia. They recommend that health care workers systematically educate and communicate with clients in order to reduce the amount of unsafe, unprotected sex; promote condom distribution in both clinical and nonclinical settings; and improve counseling services to increase clients' knowledge, perception of personal risk, and skills to negotiate condom use. ■

March 2000

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OUTSIDE FUNDING

The John D. and Catherine T. MacArthur Foundation, The Andrew W. Mellon Foundation, The Rockefeller Foundation, and the United States Agency for International Development

Microbicide Development at the Population Council — an Update

The Population Council is committed to developing and testing microbicides, products such as gels or creams that people can use vaginally or rectally before intercourse to protect themselves from acquiring sexually transmitted infections, including HIV. Carraguard™, the Council's leading candidate microbicide, is a noncontraceptive gel whose active ingredient is carrageenan, a sulfated polysaccharide found in seaweed and commonly used in food. Phase I trials have shown Carraguard to be nonirritating and easy to apply. The Council is currently conducting or planning additional Phase I safety trials with Carraguard to study safety of vaginal and rectal use in HIV-negative men and HIV-positive women and men. The Council conducted two expanded safety and acceptability trials of Carraguard between October 1999 and November 2001 in South Africa and Thailand. Final results will be available in mid-2002.

The Council will initiate a Phase III, randomized, controlled, double-blind effectiveness trial of Carraguard at four sites in southern Africa in late 2002. The primary objective of the trial is to determine the effectiveness of Carraguard in averting HIV infection when applied prior to vaginal sex. Secondary objectives are to assess the effectiveness of Carraguard in averting a range of bacterial sexually transmitted infections (STIs), such as gonorrhea, chlamydia, trichomoniasis, and syphilis, and possibly other viral STIs, such as herpes simplex virus type 2 and human papillomavirus; and to evaluate its safety, acceptability, and use dynamics when used for up to two years. The total duration of the trial is approximately four years.

STI Prevention

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inexpensive, chemically stable, nonirritating, and not absorbed by the body (to prevent side effects). Ideally, it would block infection not only by HIV, but by other STD pathogens as well.

Phillips's team recently identified a group of compounds that appear to fit these requirements: the sulfated polysaccharides—substances found in every plant and animal. Some of them block infection by chlamydia as well as HIV *in vitro*. A formulation containing one of these compounds was shown in a Phase 1 clinical trial to be nonirritating to the vagina.

Promising as these scientific advances are, "a long and costly road exists between a concept and a product," Phillips observes. More research questions must be answered, and obstacles to product testing and manufacture overcome, before microbicides take their place next to spermicides on clinic and pharmacy shelves." ■ Summer 1996

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