

HIV's Quiet Accomplice?

Imbalances in vaginal flora may link to the AIDS epidemic

By JEFFREY BRAINARD

Vaginal hygiene is a private, sensitive topic. Recently, however, at meetings and in reports, researchers have been publicly voicing concerns that an often-overlooked vaginal infection that's common among some groups of women may contribute significantly to the spread of AIDS.

Bacterial vaginosis, an annoying but seemingly harmless infection, occurs frequently among African women. It is less common in the United States, where it affects larger numbers of African Americans and Hispanics than whites.

Emerging research suggests a danger to women with vaginosis and to their male sexual partners. The troublesome bacteria that cause vaginosis, or a deficit of those that appear to guard against it, may increase the likelihood that harmful vaginal invaders, including HIV, will cause disease and be transmitted.

Diagnosing and treating bacterial vaginosis "is a very high priority for us," says Penelope J. Hitchcock, chief of the sexually transmitted diseases branch of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md. "We're concentrating now on getting better tools [to do that]. Until we have those tools, this is a tough problem."

Help may be on the way. Researchers are studying vaginal bacteria called lactobacilli that appear to protect women against vaginosis. Sharon L. Hillier of the University of Pittsburgh Magee-Women's Hospital is now testing what she calls a vaginal vitamin to restore proper concentrations of the helpful bacteria.

Over the past decade, researchers have begun to document how vaginal infections contribute to risk of more serious conditions. Bacterial vaginosis can cause itching, excessive vaginal discharge, and a fishy odor. The bacteria that cause the condition produce organic byproducts with such telling, if unsavory, names as putrescine and cadaverine. The first also emanates from rotting fish, the second from corpses. However, bacterial vaginosis does not always produce notice-

able symptoms.

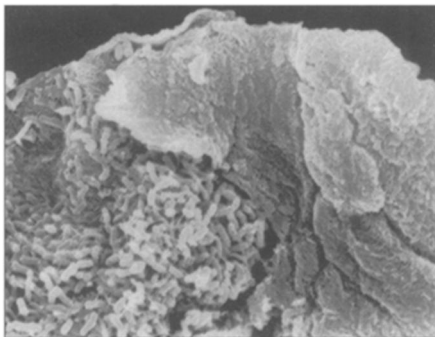
Serious damage from vaginosis was first detected in studies linking the condition to premature birth. In one of the largest, Hillier and colleagues reported in 1995 on 10,397 pregnant women examined at seven U.S. hospitals (SN: 01/13/96, p. 31). Sixteen percent of those women were diagnosed with bacterial vaginosis, and those women were 40 percent more likely to deliver prematurely than those who did not have the condition. Overall, bacterial vaginosis caused 6 percent of the early births in the study group. Premature birth is one of the leading causes of infant mortality.

Although investigators haven't determined the precise mechanism by which bacteria vaginosis leads to premature delivery, they suspect the infection disrupts the amniotic sac.

In recent years, researchers have also wondered whether bacterial vaginosis might lead to sexually transmitted diseases, including HIV. Studies have focused on Africa, where vaginosis is more prevalent than in the United States.

In one study, Ugandan and U.S. investigators examined 4,718 pregnant women in rural Uganda. They found that about 50 percent of the women had some degree of bacterial vaginosis. Furthermore, 27 percent of women with severe bacterial vaginosis carried HIV versus 14 percent without vaginosis, the researchers reported in the Aug. 23, 1997 LANCET.

A high prevalence of bacterial vaginosis may significantly boost the spread



Electron micrograph of abnormal bacterial overgrowth characteristic of vaginitis.

of AIDS, suggested study coauthor Ronald H. Gray of Johns Hopkins University in Baltimore, speaking at this summer's World AIDS Conference in Geneva. Follow-up data since the study was published suggest that among the women examined, bacterial vaginosis is implicated in 15 percent of all new HIV cases, he says.

Another study, to be published in the Sept. 12 AIDS, monitored 1,196 pregnant women in Malawi every 3 months for 2 years. Taha E. Taha of Johns Hopkins University and his colleagues report that during the study, women with severe bacterial vaginosis were 3.7 times more likely to acquire HIV than those without vaginosis.

In addition, at the Geneva conference, Harold L. Martin Jr. of the Park Nicollet Clinic in St. Louis Park, Minn., presented a study of 657 female prostitutes in Mombasa, Kenya. He and his colleagues found that bacterial vaginosis increased the risk of developing HIV during the 3-year study.

All three studies were controlled for confounding factors such as the number of sexual partners and the presence of sexually transmitted diseases known to increase HIV risk.

The contribution of vaginosis to AIDS is much higher than that of gonorrhea and syphilis, two sexually transmitted diseases that have been associated with increased risk of HIV transmission, Gray says. The sexually transmitted diseases inflame or ulcerate the vaginal wall and so put an individual woman at greater risk of acquiring HIV than does vaginosis. However, the higher incidence of vaginosis makes it a larger factor in the spread of AIDS through a population, he says.

The follow-up data from the Ugandan study also suggest that a man's risk of acquiring HIV during intercourse with an HIV-infected woman doubles when she has bacterial vaginosis. Gray estimates that this factor accounted for 15 percent of the new HIV infections in male partners of HIV-infected women in the study. Controlling vaginosis would not be "a magic bullet from an HIV [prevention] perspective, but in a population it could be very important," he says.

Health experts and doctors have begun to concentrate on fighting sexually transmitted diseases to reduce HIV transmission but have not placed the same emphasis on bacterial vaginosis. "People didn't give it much attention because they felt it is probably the normal state," Taha says.

In the United States, women of some groups have a higher than average incidence of vaginosis. In a nationwide study of 13,747 pregnant women, Hillier and her colleagues found that 23 percent of black women had vaginosis, versus 16 percent of Hispanic women and 9 percent of white women. They reported the findings in the May 1996 AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. Other stud-

ies have found that as many as 35 percent of African American and U.S. Hispanic women have vaginosis.

The AIDS epidemic is not as widespread in the United States as in Africa. So for most U.S. women, even if they are at increased risk of HIV because of bacterial vaginosis, the risk of HIV infection is still low. However, the odds are less reassuring for African American and U.S. Hispanic women. These subgroups are at higher jeopardy than other U.S. women both for contracting vaginosis and HIV. By treating and preventing vaginosis, "I think that, in fact, we could decrease the acquisition of HIV for many high-risk women," Hillier says.

Eradicating the odiferous aura of vaginosis is more complex than simply taking a pill. An inexpensive antibiotic, metronidazole, quickly extinguishes the infection, but up to 80 percent of treated women later relapse, many of them within six months. Investigators don't think that the bacteria that cause vaginosis develops into resistant strains. Rather, women may simply become reinfected.

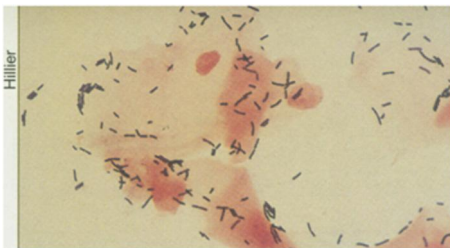
Hillier and other researchers say they do not fully understand why women get vaginosis. It does not appear to be transmitted through intercourse. However, women do have an increased risk of the condition after taking a new sexual partner, regardless of the frequency of intercourse.

Ironically, a common practice intended to promote vaginal health may be part of the problem. Hillier and her colleagues at the University of Washington in Seattle published a study in the November 1996 *JOURNAL OF INFECTIOUS DISEASES* showing that women who douched at least monthly doubled their risk of vaginosis. The researchers followed 182 women attending a Seattle clinic for sexually transmitted diseases.

What's more, two-thirds of African American women say they douche, versus one-third of white women, according to a February 1992 report in the *AMERICAN JOURNAL OF PUBLIC HEALTH*. Taha and Martin say the practice is also common among the African women they studied. Those populations may need health education to the effect that regular douching may interfere with maintaining a healthy vagina, Gray says.

Hillier is exploring other ways to help women maintain a proper balance of vaginal flora. Just as normal, healthy guts are populated by helpful organisms that aid digestion, healthy vaginas contain beneficial microbes, called lactobacilli, she says. People who lose their intestinal bacteria—say because of antibiotic treatment—can become ill; similarly, a deficit of the protective vaginal bacteria may invite overgrowth of bacteria that cause vaginosis.

Several studies in the 1990s connected



Helpful bacteria called *Lactobacillus crispatus* (shown in stained laboratory sample magnified 1800X) produce hydrogen peroxide, which may protect the vagina against harmful infections.

increased rates of vaginosis and deficiencies in the helpful lactobacilli. These beneficial organisms are cousins of the acidophilus cultures in yogurt, although the yogurt strains cannot survive in the vagina.

Some reports have demonstrated that different varieties of lactobacilli offer differing levels of protection against vaginosis. One class of strains, which Hillier has dubbed "lucky lactos," produces both lactic acid and hydrogen peroxide. Another group of lactobacilli makes only lactic acid.

"People have accused me of being crazy" for suggesting that vaginal ecology plays a role in HIV transmission, Hillier says. Evidence supporting her view came initially from a study in the July 1991 *JOURNAL OF EXPERIMENTAL MEDICINE* by Seymour J. Klebanoff and Robert W. Coombs of the University of Washington in Seattle. In test-tube experiments, they showed that lucky lactos killed HIV, whereas regular lactobacilli were ineffective. When they added an enzyme that deactivated the peroxide, the killing power of the lucky lactos fell off.

Moreover, Harold L. Martin reported at the recent AIDS conference in Geneva that Kenyan prostitutes with lucky lactos were one-third as likely to get HIV as those carrying no lactobacilli. Meanwhile, women with only non-peroxide-producing lactobacilli became infected with HIV at an intermediate rate.

That study also supported findings from Hillier's 1996 report in the *JOURNAL OF INFECTIOUS DISEASES*. She and her coauthors found that women with lucky lactos were one-fourth as likely to contract bacterial vaginosis during the study as women with no lactobacilli. They also determined that white women were more likely to possess lucky lactos than other women.

"We know very, very little about the source of these microorganisms and why some women tend to lose them so quickly," Hillier says. They appear to originate in the rectum, she adds.

Other studies suggest that a lactobacilli deficit can, in effect, cure itself: Women missing lucky lactos sometimes acquire them without medication. But with some women, the deficiency of lucky lactos recurs, and they suffer from accompanying vaginosis on a chronic basis.

To find ways to restore lactobacilli, Hillier has tested a vaginal capsule con-

taining lucky lactos. In a recently completed preliminary trial, she and her colleagues gave the capsules to 90 young women, ages 14 to 21, in the Pittsburgh area. They chose that population because young women are at especially high risk of sexually transmitted disease. Some evidence suggests that proper levels of lucky lactos protect women against gonorrhea and chlamydia as well as HIV.

Hillier and her colleagues asked the women to insert a capsule vaginally twice a day for 3 days; after 4 weeks, they tested them for lucky lactos. Of the women who had showed suboptimal levels of lucky lactos, 80 percent acquired them during the trial. Women who had more lucky lactos at the beginning of the test appeared to pick up fewer. Researchers had been concerned that the suppositories might produce a harmful overgrowth of the peroxide-producing lactobacilli, but they did not observe such an effect.

"It only gives you what you need," Hillier says. "It's like vitamin C. What you can't use just washes away."

In a 2-year, follow-up study, the scientists plan to examine whether the suppositories reduce the incidence of vaginosis and gonorrhea in a larger group of women.

Even if the trial is successful, vaginal infections will not fade away, Hillier says. Unfortunately, lucky lactos do not seem to protect against yeast infections or trichomoniasis, an infection caused by a parasitic protozoan.

In addition to better treatments, Hitchcock says women need a reliable way to tell whether they have bacterial vaginosis. The condition's symptoms resemble those of yeast infections, also called candidiasis, and trichomoniasis. But over-the-counter yeast medications don't cure bacterial vaginosis, Hitchcock says. NIAID recently funded the development of at-home tests using a self-administered swab to detect vaginosis.

Although evidence suggests a link between lactobacilli deficiency and HIV infection, Hillier and other researchers agree that the relationship has not been conclusively demonstrated. The imbalance that defines bacterial vaginosis may merely be associated with another risk factor that actually increases the risk of HIV acquisition, says Myron M. Cohen of the University of North Carolina at Chapel Hill, a question he calls "well worth study."

Until researchers perform more studies and develop effective treatments, it's too soon to call for a campaign against bacterial vaginosis to cut the spread of HIV, says Judith N. Wasserheit of the federal Centers for Disease Control and Prevention in Atlanta.

However, Wasserheit says of the findings so far, "These are very exciting data, they are very provocative, and they need to be pursued." □