HPV-Related Vulvar Diseases Persist in HIV-Positive Women

BY ELIZABETH MECHCATIE
Senior Writer

BETHESDA, MD. — HIV-infected women shed more human papilloma virus, have higher rates of high-grade cervical intraepithelial neoplasia, and are diagnosed more frequently with vulvar intraepithelial neoplasia (VIN) than are women who are not infected, Thomas C. Wright Jr., M.D., said at a conference on vulvovaginal diseases.

Women infected with HIV have an increased rate of human papilloma virus (HPV) shedding that is generally estimated at about four times that of HIV-negative women, said Dr. Wright, director of obstetrics, gynecology, and pathology at Columbia University College of Physicians and Surgeons, New York.

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DR. WRIGHT

Among HPV-infected women, those who are also infected with HIV have more HPV types than do women without HIV. In one study conducted in New York City, 31% of HIV-positive women had more than one HPV type, vs. 9% of HIV-negative women. A total of 16% and 14% had HPV 16 and HPV 18, respectively, in the HIV-positive group vs. 6% and 3%, respectively, in HIV-negative women.

Studies conducted in the 1990s determined that the distribution of HPV types in women without cervical intraepithelial neoplasia (CIN) tend to be the same in those who are HIV positive and those who are HIV negative. But women with biopsy-confirmed CIN 2,3 who are HIV positive "tend to be more heterogenous for high-risk [HPV] types" he said.

Types 16 and 18, which tend to be the most common high-risk HPV types in the general population and appear to be more aggressive than other high-risk HPV types, are found in considerable numbers of CIN 2,3 cases in both HIV-infected and uninfected women. However, in HIV-infected women, the other HPV types that can cause cancer "may become a little more pathogenic" as the immune system deteriorates, Dr. Wright noted.

Viral load and CD4 counts have both been found to be markers for patients who shed HPV: The Women's Interagency HIV Study (WIHS) published in 1999 found that HPV was detected more frequently in women with low (under 200) CD4 counts, regardless of their HIV viral load. Similarly, women with a high HIV viral load, even with a higher CD4 count, will have high rates of HPV shedding, Dr. Wright said at the conference, sponsored by the American Society for Colposcopy and Cervical Pathology.

For more than a decade, it has been clear that the prevalence of CIN among HIV-positive women is high, estimated at two to four times higher than among noninfected women. He referred to four large prospective follow-up studies, including one he and his associates conducted in New York City, which found that the rates of abnormal cytology in HIV-positive women ranged from 30% to 40%, vs. 8% to 20% among HIV-negative women.

In his study, 7% of the HIV-positive women had high-grade CIN (CIN 2,3), vs. 1% of the HIV-negative women. Over a 3-year follow-up, 20% of the HIV-positive women developed biopsy-confirmed CIN, increasing to 30% over 6 years. Predictably, a woman with low CD4 counts is more likely to develop CIN, Dr. Wright said, adding that a woman with low CD4 counts who is followed for 48 months has a 40% chance of developing biopsy-confirmed CIN.

In HIV-infected women condylomas are very common. Vulvar condylomas in this population are numerous and multifocal, and tend to respond poorly to standard treatments, he said. Although VIN is less common than is CIN, VIN is much more common in HIV-infected women compared with uninfected women.

In a study published this year of 1,778 HIV-infected women and 500 HIV-negative women followed for 8 years, incident condylomas were detected in 23% of HIV-positive women vs. 7% of HIV-negative women. In the WIHS study published this year, risk factors for condylomas identified among HIV-positive women were cytologic abnormalities, HPV, smoking, no HAART (highly active antiretroviral therapy), and a low CD4 count, he said.

Now that HAART is used so widely, there is much less cervical and vulvar disease in HIV-infected patients, Dr. Wright observed. At one point, a large proportion of the patients he saw at the Columbia colposcopy clinic were HIV positive, but those numbers have markedly dropped now that most are on HAART, which has been shown to reduce the incidence of condylomas.

VIN, however, is clearly an increasing problem in this population, he said. Because women in the HIV clinic are well screened and treated with loop electrosurgical excision procedure when CIN is detected, cervical cancer is less common. In contrast, "we continue to identify vulvar cancers," since screening and treating for VIN lesions is not as thorough.

In a study that followed cervical disease in HIV-positive and HIV-negative women, he and his coinvestigators have found that about 4% of HIV-positive women developed biopsy-confirmed VIN over 60 months vs. less than 1% of HIV-negative women. And, as with cervical disease, the risk was higher with lower CD4 counts, where almost 20% of those with CD4 counts under 200 developed biopsy-confirmed VIN.

In the WIHS study, incident VIN 2,3 was detected in 8% of HIV-positive women during follow-up and 2% of HIV-negative women, "a relatively high attack rate" of 1.52 per 100 person-years among HIV-positive women, vs. 0.36 per 100 person-years for HIV-negative women. This indicates that about 1% of HIV-positive women will develop biopsy-confirmed VIN every year, Dr. Wright pointed out.

In the WIHS study, the risk of VIN 2,3 was increased in women with cytologic abnormalities and high-risk HPV types. However, HAART use and CD4 counts did not have a significant impact on incidence, so while HAART is effective in reducing condylomas and CIN, "we're not seeing the same dramatic impact of HAART on VIN incidence, in the studies that have been reported."

Based on these findings, he recommended a high level of awareness of vulvar disease in HIV-infected patients. When an HIV-positive patient is referred with an ASCUS (atypical squamous cells of undetermined significance) and LSIL (low-grade squamous intraepithelial lesions) Pap, "be absolutely certain that you do a very careful inspection of the vulva, and do liberal biopsies" of anything that looks abnormal. ■

Drug Resistance Factors Into HIV Treatment Failures

BY HEIDI SPLETE
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BETHESDA, MD. — Drug resistance poses a problem in treating HIV patients, in part because of the virus's high mutation rate, Roy M. Gulick, M.D., said at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

Factors affecting HIV drug resistance include the virus itself, the antiretroviral drugs used, and the characteristics of the individual patient. Drug resistance is one of the main reasons why HIV treatments fail, said Dr. Gulick, director of the Cornell HIV Clinical Trials Unit at Weill Medical College of Cornell University, New York.

The goal of antiretroviral therapy (ART) is to suppress the viral load to as low a level as possible for as long as possible, he noted. Due to the high rate of mutation in the HIV virus, viral diversity is extensive. Failure to suppress viral load levels in the presence of antiretroviral drugs leads to the development of a resistant strain, Dr. Gulick explained.

Patient-related factors that can contribute to the development of resistance include the stage of disease, use of other medications, medication adherence, and side effects.

"We used to follow resistance clinically. If someone was taking their drugs, and their viral load went down, but then rose again, if we were sure that they were taking the medication, we assumed that they had developed resistance," he said. Today, genotypic tests provide viral sequencing of a patient's viral strain, and phenotypic tests can grow the patient's virus in vitro and assess resistance in the presence of the available antiretroviral drugs.

Are resistance tests clinically valuable? Dr. Gulick cited three studies, including one published in the Lancet, in which several hundred patients who had failed drug therapies were randomized to either genotypic or phenotypic drug resistance testing or standard care (Lancet 1999;353:2195-9).

Overall, the patients who fared better in terms of viral load reduction on their new regimens were the ones who had the resistance tests.

"Simply put, resistance tests help clinicians choose active drugs for the next regimen," Dr. Gulick said. Guidelines from the Department of Health and Human Services recommend resistance tests in the clinical setting in cases of virologic failure, suboptimal virologic suppression, and acute HIV infection.

These tests could be considered in cases of HIV infection before starting ART, but they are generally not recommended for patients more than 4 weeks after ART drug use ends, or when viral load levels are less than 1,000 copies per million.

However, studies of the effectiveness of resistance testing are limited by several factors, including problems with the clinical cutoffs—when the drugs lose activity over time—and questions as to whether the studies had enrolled patients who had failed multiple treatments.

Other studies have shown conflicting results regarding the use of resistance tests, especially for highly resistant patients. "The best resistance tests can't help a patient if they have no drug options to go to," Dr. Gulick said.

Asked whether he recommends genotypic or phenotypic testing for patients who are just starting antiretroviral therapy or who already have resistance, Dr. Gulick commented that although sufficient clinical evidence is lacking, most experts recommend a genotype test for patients who are treatment naive or have failed their first regimen, when it is relatively easy to figure out what the mutations mean. But in patients who have been through multiple regimens, phenotype is easier to interpret.

"Many people say that if cost is not an issue, they would get both tests, because they tell you different things—particularly in the late stages of infection," he added.