Perspective

Human Papillomavirus Infection in HIV-infected Persons

Rates of cervical and anal human papillomavirus (HPV) infection and abnormal cytology are high in HIV-infected women, as are rates of anal HPV infection and abnormal cytology in HIV-infected men who have sex with men (MSM). Available evidence indicates that the incidence of anal cancer in HIV-infected MSM has increased in association with prolonged life expectancy achieved with antiretroviral therapy. Routine screening for cervical neoplasia is recommended for HIV-infected women. Routine screening is not yet universally recommended for anal neoplasia, although it should be considered for at-risk patients, particularly given recent improvements in local treatments. A preventive vaccine against cervical HPV infection is approved for use in young women before onset of sexual activity and acquisition of HPV infection. Its potential benefit in preventing anal infection in women and men has yet to be determined, and its potential utility in those with HIV infection remains unknown. This article summarizes a presentation on HPV infection in HIV-infected patients made by Joel Palefsky, MD, at an International AIDS Society–USA Continuing Medical Education course in Chicago in May 2007. The original presentation is available as a Webcast at www.iasusa.org.

Infection with human papillomavirus (HPV) poses risk of cervical and anal cancer in women and anal cancer in men who have sex with men (MSM). There are high rates of cervical and anal HPV infection in HIV-infected women and high rates of anal HPV infection in HIV-infected MSM. Infection in the cervix primarily occurs in the transformation zone where the squamous epithelium of the exocervix and columnar epithelium of the endocervix meet. The anal canal has a similar zone where the squamous epithelium of the anus meets the columnar epithelium of the rectum. This latter structure is more exteriorized in women than in men, which may account for the apparent higher rate of anal infection in women than in men. The virus must reach the basal cell layer to initiate infection, and it is currently thought that it takes approximately 24 hours for the virus to enter these cells. This window appears to allow time for vaccine-induced antibody response that has been shown to be effective in preventing infection (see below).

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Risk of Human Papillomavirus Infection and Associated Cancer

Figure 1 shows rates of HPV cervical infection and abnormal cervical cytology in HIV-seronegative women and HIV-infected women according to CD4+ cell count, and rates of anal infection and abnormal cytology in MSM according to HIV status and CD4+ cell count. Rates of infection and abnormal cytology increase as CD4+ cell count decreases, as do the number of oncogenic HPV types involved in infection. As shown in Figure 2, data from a single study population (the Women's Interagency HIV Study) show that anal infection in women is more common than cervical infection. Studies in the general population have also shown that rates of anal infection are at least as high as rates of cervical infection in women.

HPV infection is the most common sexually transmitted infection in the general population, with it being estimated that some 75% of all sexually active adults acquire a genital HPV type during their lifetime. In immunocompetent individuals, HPV replication is usually suppressed, with relatively low rates of progression of low-grade squamous intraepithelial lesions (LSIL), which are not thought to be a cancer precursor, to high-grade squamous intraepithelial lesions (HSIL), which are believed to be a cancer precursor. In HIV infection, immune suppression is associated with higher rates of progression of LSIL to HSIL. However, it appears that immune response is not as important a determinant of progression from HSIL to cancer, with slow accumulation of genetic changes appearing to account for the prolonged

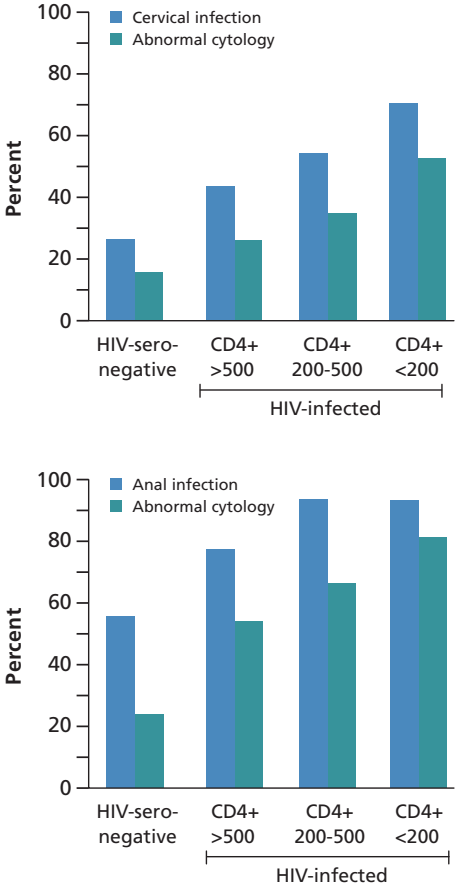

Figure **1**. Top: Rates of human papillomavirus (HPV) cervical infection and abnormal cytology in HIV-seronegative women and HIV-infected women according to CD4+ count (cells/μL). Bottom: Rates of HPV anal infection and abnormal cytology in HIV-seronegative men who have sex with men (MSM) and HIV-infected MSM according to CD4+ count (cells/μL). Adapted from Palefsky et al, *J Natl Cancer Inst,* 1999; Massad et al, *JAIDS,* 1999; Palefsky et al, *JAIDS,* 1998; and Palefsky et al, *J Infect Dis,* 1998.

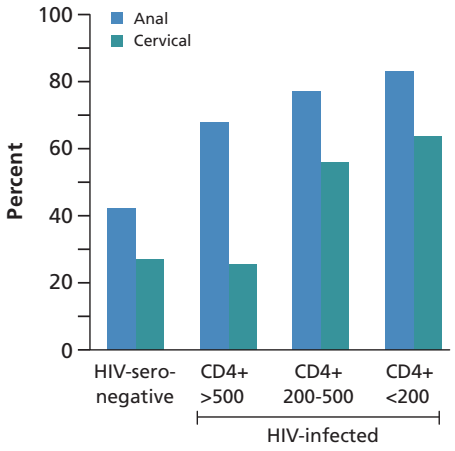

Figure 2. Rates of cervical and anal human papillomavirus infection in HIV-seronegative women and HIV-infected women according to CD4+ count (cells/μL) in the Women's Interagency HIV Study. Adapted from Palefsky et al, *J Infect Dis,* 2001.

progression (eg, 20 years) to cancer. This is supported by the finding of studies of the effect of antiretroviral therapy on cervical and anal lesions, with available data suggesting only a minor positive effect or no effect of antiretroviral therapy-associated immune reconstitution on regression of HSIL. In fact, numerous data indicate that the rate of anal cancer is increasing in HIV-infected individuals since the advent of potent antiretroviral therapy, with the prolonged life span associated with antiretroviral therapy appearing to permit progression to cancer in more patients. One recent study found that the rate of anal cancer in the general population increased from 0.6 per 100,000 population in the pre-HIV era of 1973 to 1981 to 0.8 per 100,000 in 1982 to 1995, and to 1 per 100,000 during the potent antiretroviral therapy era of 1996 to 2001 (Chiao et al, *JAIDS,* 2005). At the same time, the ratio of females to males decreased from 1.6 to 1, to 1.2 to 1. It is believed that these changes reflect an increasing incidence of anal cancer in the HIV-infected MSM population. Another study in 8640 HIV-infected MSM in London (Bower et al, *JAIDS,* 2004) showed that the rate of anal cancer increased from 35 per 100,000 person-years in the pre-antiretroviral therapy era to 92 per 100,000 person-years after introduction of antiretroviral drugs. A study matching the San Francisco AIDS Surveillance Registry and the California Cancer Registry showed that among more than 14,000 adults diagnosed with AIDS from 1990 to 2000, the risk of anal cancer increased nearly 3-fold after 1995, with likelihood of death from anal cancer also increasing somewhat during this period (Hessol et al, *Am J Epidemiol,* 2007).

Assessment Guidelines

The guidelines for assessing cervical intraepithelial neoplasia (CIN) in HIV-infected women are currently being rewritten but are expected to undergo little change. The guidelines call for a Pap test at initial evaluation and a repeated Pap test at 6 months. If both are negative, Pap testing can be repeated annually. Physicians should maintain a low threshold for performing colposcopy for findings of atypical squamous cells of unknown significance (ASCUS) or higher grades of dysplasia.

The 2005 Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), HIV Medicine Association of the Infectious Diseases Society of America guidelines for assessment of anal intraepithelial neoplasia (AIN) in HIV-infected patients state: "Although formal guidelines recommending anal Pap smear screening have not been adopted, certain specialists recommend anal cytologic screening for HIV-1-infected men and women. High-resolution anoscopy should be considered if the anal Pap smear indicates ASCUS or ASC-H [atypical squamous cells–cannot rule out HSIL] and should be performed if a person has LSIL or HSIL on anal Pap smear. Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer." These guidelines are also being rewritten, but the new guidelines also will not recommend routine screening. The recommendation for routine screening awaits evidence that screening and treatment of lesions reduces risk of progression to anal cancer.

However, some local authorities are recommending screening when it is available. For example, the New York State Department of Public Health AIDS Institute guidelines for the Primary Care Approach to the HIV-Infected Patient state: "Although this is a new practice that may not be routinely available, screening for cellular dysplasia is prudent and recommended, particularly in persons at high risk for infection with papilloma virus." The guidelines recommend that at baseline and as part of the annual physical examination of all HIV-infected adults, clinicians should: inquire about anal symptoms, such as itching, bleeding, diarrhea, or pain; perform a visual inspection of the anal region; and perform a digital rectal examination. It is further recommended that clinicians perform anal cytology at baseline and annually in MSM, in any patient with a history of anogenital condylomas, and in women with abnormal cervical or vulvar histology, and that patients with abnormal anal Pap test findings be referred for high-resolution anoscopy or examination with biopsy.

Infrastructure for treating abnormal anal findings in routine screening is currently lacking in most locales, and the value of screening in the absence of such infrastructure is questionable. However, such infrastructure should be developed, since earlier identification of abnormalities or cancer itself can result in improved outcomes. Identification of lesions early in the natural history of disease would increase the proportion of patients identified with smaller lesions; small lesions can be treated with application of trichloroacetic acid, which is well tolerated and very inexpensive. Identification of lesions during later progression—eg, the middle range of natural history of the disease—would increase the proportion of patients who could have treatment by other local modalities, avoiding the morbidity and expense associated with surgical removal. For example, infrared coagulation, an office-based treatment performed with an anoscope, has been found to result in freedom from disease in 65% of patients after median follow-up time of 413 days (Goldstone et al, *Dis Colon Rectum,* 2005).

Earlier identification of disease late in the course of progression would fa-

Table **1.** Analysis of Efficacy of Human Papillomavirus (HPV) L1 Protein Virus-like Particle Vaccine Against HPV Types 16- and 18-related Cases of Cervical Intraepithelial Neoplasia Grades 2 and 3 or Worse

	Vaccine N=10,268			Placebo N=10,273			Efficacy (95% confidence interval)
	No. of subjects	No. of cases	Incidence	No. of subjects	No. of cases	Incidence	
Per-protocol	8487	0	0	8460	53	0.4	100% (92.9–100)
Modified intent-to-treat	9831	122	0.6	9896	201	0.9	39.0% (23.3–51.7)

Per-protocol population included only women with no prior evidence of HPV infection. Modified intent-to-treat population included women with prior HPV infection. Adapted from Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant, Package Insert, 2006.

cilitate earlier diagnosis and treatment of cancer. As with cervical cancer, survival in anal cancer is better with earlier diagnosis and treatment. Treatment for anal cancer currently involves use of chemotherapy and radiation therapy, which are associated with substantial morbidity.

It must be emphasized, however, that it remains to be demonstrated that screening and treatment of AIN can reduce the incidence of anal cancer. It is likely that routine screening will not be universally recommended until such evidence is available. Even in the absence of infrastructure for screening and treatment of AIN, all at-risk men and women should be screened for anal cancer by digital rectal exam.

Human Papillomavirus Vaccines

The currently available preventive HPV vaccine is a quadrivalent virus-like particle vaccine covering HPV types 16 and 18, implicated in approximately 70% of cervical cancers worldwide, and covering types 6 and 11, which cause genital warts. In women with no serologic or DNA evidence of HPV type 16 or 18, the vaccine was 100% effective in preventing CIN grades 2 and 3 or worse due to these HPV types (Garland et al, *N Engl J Med,* 2007). In an intent-to-treat analysis including women with prior exposure to HPV, vaccine efficacy was 39% (see Table 1). The vaccine is currently recommended in the United States for young women prior to onset of sexual activity (eg, ages 11 or 12 years), who thus are unlikely to have had prior HPV infection. The vaccine was also 99% effective in preventing genital warts. In intent-to-treat analysis including women with prior exposure to HPV, vaccine efficacy was 12.2% in preventing CIN grades 2 and 3 or worse due to any HPV type. Although, again, the study population was not similar to the current target population of young women, the finding emphasizes the fact that infection with HPV types not covered by the vaccine is still possible, and that it is still necessary for vaccinated individuals to receive annual Pap screening. Thus far, the vaccine appears safe. It is currently unknown whether booster doses are needed. Other preventive HPV vaccines are in development, including one designed to protect against infection with HPV 16 and HPV 18, and in phase III trials has been shown to be highly effective to prevent initial infection with these HPV types as well as to prevent development of CIN grades 2 to 3 associated with HPV 16 and HPV 18 in women who had not yet been exposed to these types (Paavonen et al, *Lancet,* 2007). The vaccine is currently being reviewed for approval by the US Food and Drug Administration (FDA).

With regard to potential use in HIV-infected individuals, several issues need to be clarified, including safety, whether there are sufficient numbers of HIV-infected individuals who are not HPV-infected already to provide for vaccine efficacy, and whether HIV-infected individuals can mount and maintain protective antibody titers against HPV. It is currently unclear whether the vaccine protects against anal HPV infection and AIN, although studies regarding this are underway. It should also be considered whether all men should be vaccinated before the start of sexual activity to prevent penile infection (and thus transmission to sexual partners, be they men or women) and to prevent anal infection in MSM, as well as to interrupt the cycle of transmission.

Conclusion

The incidence of AIN and anal cancer is high among HIV-infected women and MSM. Antiretroviral therapy has a limited positive effect on HPV-related neoplasia, and there is mounting evidence that the incidence of anal cancer will continue to rise among HIV-infected MSM. At-risk men and women should be considered for screening and treatment of AIN, particularly since local treatments are improving. All at-risk men and women should be screened for anal cancer by digital rectal exam, since real benefits accrue from early detection of cancer. Data are awaited to determine whether HPV vaccines can prevent anal HPV infection, AIN, and anal cancer.

Suggested Reading

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