Immune Response to HPV Infection A cell-mediated immune response plays an important role in controlling the progression of natural HPV infection. Histologic examination of lesions in individuals who experience regression of genital warts demonstrates infiltration of T cells and macrophages. CD4+ T cell regulation is particularly important in controlling HPV infections, as evidenced by the higher rates of infection and disease among immunosuppressed individuals, particularly those who are infected with HIV. Specific T-cell responses may be measured against HPV proteins, the most important of which appear to be the E2 and E6 proteins. In women with HPV-16 cervical infection, a strong T-cell response to HPV-16-derived E2 protein is associated with a lack of progression of cervical disease.

Natural HPV infection of the genital tract gives rise to a serum antibody response in only 60–70% of individuals because there is no viremic phase during infection. Significant, although incomplete, protection against type-specific reinfection is associated with the presence of neutralizing antibodies. Serum antibodies likely reach the cervical epithelium and secretions by transudation and exudation. Therefore, protection against infection is related to the amount of neutralizing antibody at the site of infection and lasts as long as levels of neutralizing antibodies are sufficient.

EPIDEMIOLOGY AND NATURAL HISTORY OF HPV-ASSOCIATED MALIGNANCY

General Population HPV is transmitted by sexual intercourse, by oral sex, and possibly by touching of a partner's genitalia. In cross-sectional and longitudinal studies, ~40% of young women have evidence of HPV infection, with peaks during the teens and early twenties—soon after first coitus. The number of lifetime sexual partners correlates with the likelihood of HPV infection and the subsequent risk of HPV-associated malignancy. HPV infection may develop in a monogamous person whose partner is infected. Most HPV infections become undetectable after 6–9 months. However, with prolonged follow-up and frequent sampling, the same HPV types may again be detected weeks or months after becoming undetectable. Whether such episodic detection indicates viral latency followed by reactivation or reinfection with an identical HPV type is still debated.

Although HPV is the causative agent of several cancers, most attention has focused on cervical cancer—the second most common cancer among women worldwide, which affects more than 500,000 women and kills more than 275,000 women annually. More than 85% of all cervical cancer cases and deaths occur in women living in low-income countries, especially in sub-Saharan Africa, Asia, and South and Central America. A quarter-century of evidence shows that HPV causes nearly 100% of cervical cancers. HPV infection is the most significant risk factor for cervical cancer; relative risks range from 10 to 20 and exceed 100 in prospective and case-control studies, respectively. The time from HPV infection to cervical cancer diagnosis may exceed 20 years. Cervical cancer peaks in the fifth and sixth decades of life among women living in developed countries but as much as a decade earlier among women living in resource-poor countries. Persistent carriers of oncogenic HPV types are at greatest risk for high-grade cervical dysplasia and cancer. Why only certain HPV infections eventually lead to malignancy is not clear. Biomarkers that can predict which women will develop cervical cancer are not available. Immunosuppression in general plays a significant role in re-detection/reactivation of HPV infections, while other factors such as smoking, hormonal changes, *Chlamydia* infection, and nutritional deficits promote viral persistence and cancer.

The International Agency for Research on Cancer concludes that HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are carcinogenic in the uterine cervix. HPV-16 is particularly virulent and causes 50% of cervical cancers. Worldwide, HPV-16 and HPV-18 cause 70% of cervical squamous cell carcinomas and 85% of cervical adenocarcinomas. Oncogenic types other than HPV-16 and HPV-18 cause the remaining 30% of cervical cancers. HPV-16 and HPV-18 also cause nearly 90% of anal cancers worldwide. Although oncogenic HPV infection is necessary for the development of cervical malignancy, only ~3–5% of infected women will ever develop this cancer, even in the absence of cytologic screening.

In addition to cervical and anal cancer, other HPV-associated cancers include vulvar and vaginal cancer, which are associated with HPV in 50–70% of cases; penile cancer, which is caused by HPV in 50% of cases; and oropharyngeal squamous cell carcinoma (OPSCC). Over the past two decades, an epidemic of OPSCC related to oncogenic infection with HPV (primarily HPV-16) has developed. Annual rates of OPSCC among men in the United States have been increasing from a low of 0.27 case/100,000 in 1973 to 0.57 case/100,000 as of 2004; rates in women have remained relatively stable at ~0.17 case/100,000 per year. The increase in the incidence of OPSCC is greatest among white men 40–50 years of age. Nearly 14,000 new cases were diagnosed in the United States in 2013. Annual rates of OPSCCs of the base of the tongue and the tonsil have increased dramatically—i.e., by 1.3% and 0.6%, respectively. Fewer data are available from developing countries about OPSCCs.

Effects of HIV on HPV-Associated Disease HIV infection accelerates the natural progression of HPV infections. HIV-infected persons are more likely than other individuals to develop genital warts and to have lesions that are more recalcitrant to treatment. HIV infection has been consistently associated with precancerous cervical lesions, including low-grade cervical intraepithelial neoplasia (CIN) and CIN 3, the immediate precursor to cervical cancer. Women with HIV/AIDS have significantly higher rates of cervical cancer and of subsets of some vulvar, vaginal, and oropharyngeal tumors than women in the general population. Studies indicate a direct relation between low CD4+ T lymphocyte counts and the risk of cervical cancer. Some studies show a reduced likelihood of HPV infection and precancerous lesions of the cervix in HIV-infected women receiving antiretroviral therapy (ART). The incidence of cervical cancer among HIV-infected women has not changed significantly since ART was introduced, possibly because of preexisting oncogenic HPV infections.

The burden of HPV-related cancers is expected to increase in HIV-infected patients, given the prolonged life expectancies made possible by ART. For women living in developing countries where cervical cancer screening is not widely available, this situation may have significant consequences. Thus, elucidating the interactions of HIV infection and cervical cancer with cofactors such as diet, other sexually transmitted infections, and environmental exposures is a research focus with potentially enormous implications for women living in low- and middle-income countries.

Similar to that of cervical cancer, the incidence of anal cancer is strongly influenced by HIV infection. HIV-infected men who have sex with men (MSM) and HIV-infected women have much higher rates of anal cancer than HIV-uninfected populations. Specifically, the incidence has been found to be as high as 130 cases/100,000 among HIV-positive MSM as opposed to only 5 cases/100,000 among HIV-negative MSM. The advent of ART has not impacted the incidence of anal cancer and high-grade anal intraepithelial neoplasia in the HIV-infected population.

More information on screening, prevention, and treatment in the HIV-infected population can be found at the Department of Health and Human Services website (*aidsinfo.nih.gov/guidelines*).

CLINICAL MANIFESTATIONS OF HPV INFECTION

HPV infects the female vulva, vagina, and cervix and the male urethra, penis, and scrotum. Perianal, anal, and oropharyngeal infections occur in both genders. **Figures 222-1, 222-2, and 222-3** show vulvar, penile, and perianal warts, respectively. Genital warts are caused primarily by HPV-6 or HPV-11; their surface is either smooth or rough. Penile genital warts are usually 2–5 mm in diameter and often occur in groups. A second type of penile lesion, keratotic plaques, is slightly raised above the normal epithelium and has a rough, often pigmented surface. Vulvar warts are soft, whitish papules that either are sessile or have multiple fine, finger-like projections. These lesions are most often located in the introitus and on the labia. In nonmucosal areas, lesions