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203 Human Papillomavirus Infections

HUMAN BOCAPARVOVIRUSES ■ ■DEFINITION Human bocavirus 1 (HBoV1) of the genus Bocaparvovirus, discovered in 2005, causes both upper and lower respiratory tract infections in young children and affects almost all children before the age of 5 years. Three related bocaviruses, HBoV2, HBoV3, and HBoV4, are mainly found in fecal samples and are thus considered enteric, with disputed roles in gastroenteritis. ■ ■EPIDEMIOLOGY HBoVs are very common worldwide; the seroprevalences in Europe, already at 6 years of age, are 80% for HBoV1, 50% for HBoV2, 10% for HBoV3, and 0–1% for HBoV4, the latter being slightly more prevalent in China. ■ ■CLINICAL MANIFESTATIONS AND DIAGNOSIS HBoVs cause systemic infections with short viremia and induction of antibodies, which can be cross-reacting between the four HBoVs. HBoV1 causes mild to severe, rarely even life-threatening, respiratory tract infections (RTIs) in 0.5- to 5-year-old children (mean 2 years); it is the second to fourth most common finding (2–20%) in nasopharyn geal secretions of pediatric RTI patients. HBoV1 DNA, in decreasing levels, often remains detectable by sensitive PCRs in the airways for weeks or months after acute RTI, which is problematic, since RTI is commonly diagnosed by qualitative PCRs in respiratory secretions. This may lead to clinically incorrect interpretations of etiology, codetections with other respiratory pathogens, and doubts of the role of HBoV1 in pathogenesis. However, clinical disease due to HBoV1 is associated with evidence of acute primary infection based on other diagnostic methods: sole infection, serology (IgG seroconversion or fourfold or greater increase in titer, IgM positivity, and/or low IgG avidity), viremia, and presence in respiratory secretions of spliced viral mRNA, high-load HBoV1 DNA (>104 genome copies/mL), or antigens. A combination of these methods should be applied in cases of severe or uncommon disease manifestations or for epidemiologic studies. HBoV1 causes both upper and lower RTIs, such as common cold, bronchiolitis, pneumonia, and exacerbations of asthma, with symptoms similar to those of other viral RTIs, with fever, cough, and wheezing commonly reported. In addition, diarrhea and acute otitis media often complicate HBoV1 infection. The role of the enteric HBoVs in childhood gastroenteritis remains to be established, but they have, like HBoV1, also been shown to cause encephalitis. There are no specific treatments or vaccines for HBoV infections. OTHER HUMAN PARVOVIRUSES ■ ■BUFA- AND CUTAVIRUSES Bufavirus and cutavirus of the genus Protoparvovirus were recently discovered in diarrheal stools by metagenomics. The global serop revalence of bufavirus varies extensively from 3 to 85%, whereas that of cutavirus remains <6%. Although bufavirus DNA is found in 0.2–4% of diarrhea stools, the viral loads are low, and its pathogenic role is disputed. Interestingly, skin-persistent cutavirus has been shown to be associated with cutaneous T-cell lymphoma and its precursor, para psoriasis en

plaques, the latter with up to 67% genoprevalence in skin biopsies. Whether this association is causal or consequential remains to be confirmed. ■ ■PARVOVIRUS 4 Parvovirus 4 (parv4), in the genus Tetraparvovirus, was initially discov ered in a patient with an acute viral syndrome and has since been found in pooled plasma donations and blood or tissues of injection drug users and hemophiliacs, suggesting parenteral spread. Even though parv4 in general is considered apathogenic, occasional studies have detected its DNA in patients with rash and respiratory, gastrointestinal, or central nervous system infections. ■ ■ADENO-ASSOCIATED VIRUSES Adeno-associated viruses (AAV, with many serotypes), of the genus Dependoparvovirus, depend on helper functions from other viruses

for their replication. Because of their ability to remain latent and their apathogenic nature, they have been developed as successful vectors in gene therapy. Nevertheless, in 2022, AAV2 was surprisingly associated with acute childhood hepatitis, but a causative role was not confirmed.

Acknowledgment I thank the previous author, Kevin E. Brown, who wrote the prior edition’s chapter. Some material from that chapter has been retained here. ■ ■FURTHER READING Christensen A et al: Human bocaviruses and paediatric infections. Lancet Child Adolesc Health 3:418, 2019. Crabol Y et al: Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus B19 infection: A retrospec tive study of 10 patients and review of the literature. Clin Infect Dis 56:968, 2013. Maple PA et al: Identification of past and recent parvovirus B19 infection in immunocompetent individuals by quantitative PCR and enzyme immunoassays: A dual-laboratory study. J Clin Microbiol 52:947, 2014. Matthews PC et al: Human parvovirus 4 ‘PARV4’ remains elusive despite a decade of study F1000 Res 6:82, 2017. Phan T et al: Cutavirus: A newly discovered parvovirus on the rise. Infect Gen Evol 80:104175, 2020. Qiu J et al: Human parvoviruses. Clin Microbiol Rev 30:43, 2017. Söderlund-Venermo M: Emerging human parvoviruses: The rocky road to fame. Ann Rev Virol 6:71, 2019. Xiuong Y et al: The risk of maternal parvovirus B19 infection during CHAPTER 203 pregnancy on fetal loss and fetal hydrops: A systematic review and meta-analysis. J Clin Virol 114:12, 2019. Human Papillomavirus Infections Darron R. Brown, Aaron C. Ermel

Human Papillomavirus

Infections Interest in human papillomavirus (HPV) infection began in earnest in the 1980s after Harold zur Hausen postulated that infection with these viruses was associated with cervical cancer. It is now recognized that HPV infection of the human genital tract is extremely common and causes clinical conditions ranging from asymptomatic infection to genital warts (condylomata acuminata); dysplastic lesions and invasive cancers of the anus, penis, vulva, vagina, and cervix; and a subset of oropharyngeal cancers. This chapter describes the epidemi ology of HPV as a virus and a pathogen, the natural history of HPV infections and associated cancers, strategies to prevent infection and HPV-associated disease, and treatment modalities for some conditions caused by HPV. ■ ■PATHOGENESIS Overview HPV is an icosahedral, nonenveloped, 8000-basepair, double-stranded DNA virus with a diameter of 55 nm. Like the genomes of other papillomaviruses, HPV’s genome consists of an early (E) gene region, a late (L) gene region, and a noncoding region, which contains regulatory elements. The E1, E2, E5, E6, and E7 pro teins are expressed early in the growth cycle and are necessary for viral replication and cellular transformation. The E6 and E7 proteins are responsible for malignant transformation, targeting the human cellcycle regulatory

molecules p53 and Rb (retinoblastoma protein) for degradation, respectively. Translation of the L1 and L2 transcripts and splicing of an E1^E4 transcript occur later. The L1 gene encodes the

54-kDa major capsid protein that makes up the majority of the virus shell; the 77-kDa L2 minor protein contributes a smaller percentage of the capsid mass.

More than 200 HPV types have been identified and are numerically designated on the basis of a unique L1 gene sequence. Approximately 40 HPV types are regularly identified in the anogenital tract; these types are subdivided into high-risk and low-risk categories depending on the associated risk of cervical cancer. For example, HPV types 6 and 11 cause genital warts and ~10% of low-grade cervical lesions and are thus designated low risk. HPV types 16 and 18 cause dysplastic lesions and a high percentage of invasive cancers of the cervix and are there fore considered high risk. HPV is a tissue-tropic virus and targets basal keratinocytes of specific anatomic tissues after microtrauma allows exposure of these cells to the virus. HPV 1, for example, causes plantar warts but does not infect genital epithelium. The HPV replication cycle is completed as keratinocytes undergo differentiation. Virions are assembled in the nuclei of differentiated keratinocytes and can be visualized by electron microscopy. Infection is transmitted by contact with virus contained in these desquamated keratinocytes (or with free virus) from an infected individual. The Immune Response to HPV Infection Unlike many viral infections, HPV infection has no viremic phase. This lack of viremia may account for the incomplete antibody response to HPV infec tion. Natural HPV infection of the genital tract gives rise to a detect able serum antibody response in 60–70% of individuals. Significant, although incomplete, protection against type-specific reinfection is associated with the presence of neutralizing antibodies. Serum anti bodies likely reach the cervical epithelium and secretions by transuda tion and exudation. Therefore, protection against infection relates to the amount of neutralizing antibody at the site of infection and lasts as long as sufficient levels of neutralizing antibodies are present. PART 5 Infectious Diseases A cell-mediated immune response plays an important role in controlling progression of HPV infection. Histologic examination of lesions in individuals who experience regression of genital warts demonstrates infiltration by 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 in immunosup pressed individuals, particularly those who are infected with HIV. Spe cific 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 HPV16 cervical infection, a strong T cell response to HPV16–derived E2 protein is associated with a lack of progression of cervical disease. However, measurable changes occur in the innate and adaptive immune systems of patients with HPV-associated cancers. There is suppression of the antigen-presentation process as well as suppression of antitumor activity. The end result is a reduction of HPV-specific antitumor immune responses and an increase in immunosuppressive cellular responses. ■ ■THE NATURAL HISTORY OF HPV-ASSOCIATED MALIGNANCY HPV is transmitted by vaginal or anal intercourse, by oral sex, and probably by touching a partner’s genitalia. In cross-sectional and longitudinal studies, ~50% of young women demonstrate evidence of HPV infection, with peaks during the teens and early twenties, within a few months after first coital experience. The number of lifetime sexual partners correlates with the likelihood of HPV infection and the subse quent risk of HPV-associated malignancy. HPV infection may occur in a monogamous person if that person’s partner is infected. Most HPV infections become undetectable after 6 to 9 months, a phenomenon known as “clearance.” However, with prolonged followup and frequent sampling, the same HPV types may

again be detected months or even years later. It is still debated whether such episodic detection indicates viral latency followed by reactivation or represents reinfection with an identical HPV type. Most evidence indicates that reactivation of latent virus is the cause of episodic detection of a spe cific HPV type.

While HPV is the causative agent of several cancers, most attention has focused on cervical cancer, which is the second most common cancer in women worldwide. More than 600,000 women are diagnosed and 300,000 die from invasive cervical cancer annually. More than 85% of all cervical cancer cases, as well as deaths, occur in women living in low-income countries, especially countries in sub-Saharan Africa, Asia, and South and Central America. Evidence collected over 25 years shows that HPV causes nearly 100% of cervical cancers. Persistent HPV infection is the most significant risk factor for cervical cancer; relative risks range from 10 to 20 and exceed 100 in case–control studies and prospective studies, respectively. The time from HPV infection to cervical cancer may exceed 20 years. Cer vical cancer peaks in the fifth and sixth decades of life for women living in developed countries and a decade or more earlier for women living in resource-poor countries. Persistent carriers of oncogenic HPV types are at greatest risk for high-grade cervical dysplasia and cancer. Why HPV infections in some women but not others eventually lead to malignancy is not clear. 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. Biomarkers that can predict which women will develop cervical cancer are not available, or incompletely char acterized. Immunosuppression in general plays a significant role in redetection/reactivation of HPV infections, while other factors, such as smoking, hormonal changes, chlamydial infection, and nutritional deficits, have an impact on viral persistence and cancer. The International Agency for Research on Cancer (IARC) has con cluded that HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are carcinogenic in the uterine cervix. HPV type 16 is particularly virulent and causes at least 50% of cervical cancers. Worldwide, HPV types 16 and 18 cause at least 70% of cervical squamous cell carcinomas and 85% of cervical adenocarcinomas. Oncogenic types other than 16 or 18 cause the remaining 30% of cervical cancers. HPV types 16 and 18 also cause nearly 90% of anal cancers worldwide. In addition to cervical and anal cancer, other HPV-associated can cers include vulvar and vaginal cancer (caused by HPV in 50–70% of cases), penile cancer (caused by HPV in 50% of cases), and at least 65% of oropharyngeal squamous cell carcinomas (OPSCCs). Over the past two decades, an epidemic of OPSCC related to oncogenic HPV infection, primarily HPV type 16, has developed. Rates of OPSCC in the United States have been increasing in men from a low of 0.27 case per 100,000 in 1973 to 0.57 case per 100,000 per year in 2004; rates in women have remained relatively stable at ~0.17 per 100,000 per year. The greatest increase in the incidence of OPSCC is among white men 40–50 years of age. Nearly 14,000 new cases were diagnosed in the United States in 2013. OPSCCs of the base of the tongue and tonsil cancer have increased annually by rates of 1.3 and 0.6%, respectively. Few data are available from developing countries about OPSCC. ■ ■THE EFFECTS OF HIV ON HPV-ASSOCIATED DISEASE HIV infection accelerates the natural history of HPV infections. HIVinfected individuals are more likely than other individuals to develop genital warts, and their lesions are more recalcitrant to treatment. HIV infection has been consistently associated with precancerous cervi cal lesions, including low-grade cervical intraepithelial lesions (CIN) and CIN 3, the immediate precursor to cervical cancer. Women with HIV/AIDS have significantly higher rates of cervical cancer as well as subsets of some vulvar, vaginal, and oropharyngeal tumors (Chap. 75) than women in the general population. Studies indicate a direct rela tionship between low CD4+ T

lymphocyte count and the risk of cervi cal cancer. Some studies show a reduced likelihood of HPV infection and precancerous lesions of the cervix in HIV-infected women given antiretroviral therapy (ART). However, the incidence of cervical cancer in HIV-infected women has not changed significantly since ART was introduced, possibly because of preexisting oncogenic HPV infections that occurred before ART was initiated. The burden of HPV-associated cancers is expected to increase in HIV-infected patients, given the prolonged life expectancies provided

with ART. For women living in developing countries where cervical cancer screening is not widely available, this trend will have significant consequences. Thus, elucidating the interactions of HIV infection and cervical cancer with cofactors such as diet, other sexually transmit ted infections, and environmental exposures is an important focus of research that impacts 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 among HIV-infected MSM has been found to be as high as 130 cases per 100,000 as opposed to 5 cases per 100,000 among HIVnegative MSM. The advent of ART has not impacted the incidence of anal cancer and high-grade anal intraepithelial neoplasia in the HIVinfected patient population. More information regarding screening, prevention, and treatment in the HIV-infected population can be found at the Department of Health and Human Services website (https://clinicalinfo.hiv.gov/en/ guidelines). ■ ■CLINICAL MANIFESTATIONS OF HPV INFECTION HPV infects the male urethra, penis, and scrotum and the female vulva, vagina, and cervix. Perianal, anal, and oropharyngeal infections occur in both genders. Genital warts are caused primarily by HPV type 6 or 11 and appear as soft sessile growths with a surface that is either smooth or rough with multiple finger-like projections. Penile genital warts are usually 2–5 mm in diameter and often occur in groups. A second type of penile lesion, the keratotic plaque, is slightly raised above normal epi thelium and has a rough, often pigmented surface. Figs. 203-1 to 203-3 show vulvar and vaginal, penile, and perianal warts, respectively. Vulvar warts are soft, whitish papules that are either sessile or have multiple fine, finger-like projections. These lesions are most often located in the introitus and labia. In nonmucosal areas, vulvar lesions are similar in appearance to those in men: dry and keratotic. Vulvar lesions can appear as smooth, sometimes pigmented papules that may coalesce. Vaginal lesions appear as multiple areas of elongated papillae. Biopsy of vulvar or vaginal lesions may reveal malignancy; differentia tion based on clinical exam is not always reliable. Subclinical cervical HPV infections are common, and the cervix may appear normal on examination. Cervical lesions often appear FIGURE 203-1 Warts of the vulva and vagina caused by human papillomavirus. (Reproduced with permission from K Wolff et al: Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York: McGraw-Hill, 2013.)

FIGURE 203-2 Penile genital warts caused by human papillomavirus. (Reproduced with permission from K Wolff et al: Fitzpatrick’s Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York: McGraw-Hill, 2013.) as papillary proliferations near the transformation zone. Irregular vascular loops are present beneath the surface epithelium. Patients who develop cervical cancer from HPV infection may present with a variety of symptoms. Early carcinomas appear eroded and bleed eas ily. More advanced carcinomas present as ulcerated lesions or as an exophytic cervical mass. Some cervical carcinomas are in the cervical canal and may be difficult to see. Bleeding, symptoms of a mass lesion in late stages, and metastatic disease that may manifest as bowel or bladder obstruction due to direct extension of the tumor also have been described. CHAPTER 203 Patients

with squamous cell cancer of the anus (Chap. 86) have more variable presentations. The most common presentations include rectal bleeding and pain or a mass sensation. Twenty percent of patients who are diagnosed with anal cancer may not present with any specific symptoms at the time of diagnosis, and the lesion is found fortuitously. Human Papillomavirus Infections ■ ■PREVENTION OF HPV INFECTION AND DISEASE Behaviors That Can Reduce Exposure to HPV HPV infec tions are transmitted through direct contact with infected genital skin FIGURE 203-3 Perianal warts caused by human papillomavirus. (Reproduced with permission from K Wolff et al: Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 8th ed. New York: McGraw-Hill, 2013.)

or mucosal surfaces and secretions. Abstinence may possibly reduce HPV infections: for both men and women, numerous studies indicate that HPV infection and HPV-associated diseases correlate with the number of lifetime sexual partners, and people with no history of sexual intercourse have a lower detection rate of HPV. Fewer studies look at nonpenetrative sex on the risk of HPV infection and disease, but several studies indicate that HPV can be spread by any sexual intimacy, including touching, oral sex, or use of sex toys. It is therefore possible that individuals who have not partaken in sexual intercourse can become infected.

Use of latex condoms reduces the risk of HPV infection and HPVassociated disease, such as genital warts and cervical precancers. Correct and consistent condom use has also been associated with regression of CIN in women and regression of HPV-associated penile lesions in men. As a preventive measure, condom use should be con sidered partially effective at best and not a substitute for cervical cancer screening or vaccination against HPV. HPV Vaccines The development of HPV vaccines effective in preventing infection and HPV-associated disease represents a major development in the past decade. The vaccines use virus-like particles (VLPs) that consist of the HPV L1 major capsid protein. The L1 protein self-assembles into VLPs when expressed in eukaryotic cells (i.e., yeast or insect cells). These VLPs contain the same epitopes as actual HPV virions. However, they do not contain genetic material and therefore cannot transmit infection. The immunogenicity of the HPV vaccines relies on development of conformational neutralizing antibodies directed toward epitopes displayed on viral capsids. Several large vaccine trials have been completed and demonstrate the high degree of safety and efficacy of HPV vaccines. There have been three HPV vaccines developed, tested, and U.S. Food and Drug Administration (FDA) approved, as described below. PART 5 Infectious Diseases BIVALENT VACCINE (CERVARIX) The bivalent HPV vaccine con tains L1 VLPs of HPV types 16 and 18 and is marketed under the name of Cervarix (GlaxoSmithKline). This vaccine was tested in 18,644 women 15−25 years of age residing in the United States, South America, Europe, and Asia. It is administered by intramuscular injec tion three times (months 0, 1, and 6). The primary endpoints of the study included vaccine efficacy against persistent infections with HPV types 16 and 18. Investigators also assessed vaccine efficacy against CIN grade 2 or higher due to HPV 16 and 18 in women who had no evidence of HPV 16 or 18 infection at baseline. Vaccine efficacy related to HPV 16 or HPV 18 was 94.9% (95% confidence interval [CI], 87.7–98.4%) against CIN 2 or worse; 91.7% (95% CI, 66.6–99.1%) against CIN 3 or worse; and 100% (95% CI, –8.6–100%) against adeno carcinoma in situ (AIS). Adverse events associated with the bivalent vaccine were evaluated in phase 3 trials in a subset of 3077 women who received vaccine and 3080 women who received hepatitis A vaccine. Injection-site adverse events (pain, redness, and swelling) and systemic adverse events (fatigue, headache, and myalgia) were reported more frequently in the HPV vaccine group than in the control group. Seri ous

adverse events, new-onset chronic disease, or medically significant conditions occurred in the same proportion (3.5%) of HPV vaccine recipients and control vaccine recipients. The bivalent HPV vaccine is approved in the United States for prevention of cervical cancer, CIN2 or worse, AIS, and CIN 1 caused by HPV types 16 and 18. This vaccine is approved for females 9−25 years of age. Cervarix is not currently marketed in the United States. QUADRIVALENT VACCINE (GARDASIL) The quadrivalent L1 VLP vaccine (HPV types 6, 11, 16, and 18) is marketed under the name Gardasil (Merck). It is administered intramuscularly three times (months 0, 2, and 6). A combined efficacy analysis based on data from four randomized double-blind clinical studies including >20,000 participants was performed; results demonstrated that vaccine effi cacy against external genital warts was 98.9% (95% CI, 93.7−100%). Vaccine efficacy was 95.2% (95% CI, 87.2−98.7%) against CIN; 100% (95% CI, 92.9−100%) against type 16- or 18-related CIN 2/3 or AIS; and 100% (95% CI, 55.5−100.0%) against type 16- or 18-related vulvar

intraepithelial neoplasia grades 2 and 3 (VIN 2/3) and against vaginal intraepithelial neoplasia grades 2 and 3 (VaIN 2/3). Safety data on the quadrivalent HPV vaccine are available from at least seven clinical trials, including nearly 12,000 women 9–26 years of age who received the vaccine and ~10,000 women who received aluminum-containing or saline placebo. A larger proportion of young women reported injection-site adverse events in the vaccine groups than in the placebo groups. Systemic adverse events were reported by similar proportions of vaccine and placebo recipients and were described as mild or moderate for most participants. The types of serious adverse events reported were similar for the two groups. Ten persons who received the quadrivalent vaccine and seven persons who received placebo died during the course of the trials; no deaths were considered to be vaccine related. During the course of studies on the quadrivalent HPV vaccine, surveillance data for development of new medical conditions were collected for up to 4 years after vaccination. No statistically significant differences in the incidence of any medical conditions between vaccine and placebo recipients were demonstrated; this result indicated a very high safety profile for the vaccine. A recent safety review by the FDA and the Centers for Disease Control and Prevention (CDC) exam ined events related to Gardasil that had been reported to the Vaccine Adverse Events Reporting System (VAERS). The adverse events were consistent with what was seen in previous safety studies of the vaccine. Of note, rates of syncope and venous thrombotic events were higher with Gardasil than those usually observed with other vaccines. The quadrivalent HPV vaccine is approved for (1) vaccination of females ages 9−26 years of age to prevent genital warts and cervical cancer caused by HPV types 6, 11, 16, and 18; (2) vaccination of the same population to prevent precancerous or dysplastic lesions, including cervical AIS, CIN 2/3, VIN 2/3, VaIN 2/3, and CIN 1; (3) vaccination of males 9−26 years of age to prevent genital warts caused by HPV types 6 and 11; and (4) vaccination of patients ages 9−26 years to prevent anal cancer and associated precancerous lesions due to HPV types 6, 11, 16, and 18. While the duration of protection has not been established, no evidence of waning protection has been found after a three-dose series of the quadrivalent HPV vaccine, even after 10 years of follow-up from clinical trials. The quadrivalent HPV vaccine is no longer available in the United States but is still available in many other countries, although production is not likely to continue in the future. NINE-VALENT VACCINE (GARDASIL-9) In 2014, the FDA approved a new nine-valent L1 VLP vaccine. The nine-valent vaccine is marketed under the name Gardasil-9 (Merck). It is administered intramuscularly two times (months 0 and 6) for males and females from age 9 to the fifteenth birthday, then three times (months 0, 2, and 6) for males and females from age 15 through age 45. Three doses of HPV vaccine are recommended for persons starting the vaccination series on or after the fifteenth

birthday and for persons with certain immunocompromising conditions, including HIV/AIDS. The nine-valent vaccine targets HPV types 6, 11, 16, and 18 (the types also targeted by the quadrivalent HPV vaccine) as well as five additional oncogenic HPV types (31, 33, 45, 52, and 58). HPV types 16 and 18 together cause up to 80% of all cervical cancers worldwide, and worldwide data show that HPV types 31, 33, 35, 45, 52, and 58 are the next most frequently detected types in invasive cervical cancers. Mathematical models estimate that the level of protection conferred by the nine-valent HPV vaccine against all HPV-associated squamous cell cancers worldwide could be raised to at least 90%. In clinical studies of females 16−26 years of age, the nine-valent HPV vaccine generated a noninferior antibody response to HPV types 6, 11, 16, and 18 compared with the quadrivalent HPV vaccine. Bridging immunologic studies in male and female vaccine recipients 9−15 years of age and in males 16−26 years of age indicated that the lower bound of the 95% CIs of the geometric mean titer ratio and seroconversion rates met criteria for noninferiority for all HPV types represented in the vaccine. In female recipients 16−26 years of age, vaccine efficacy against the combined endpoint of high-grade cervi cal, vulvar, or vaginal disease caused by any of the five additional

oncogenic HPV types was 96.7% (95% CI, 80.9–99.8%). Like the other available HPV vaccines, the nine-valent HPV vaccine is safe and extremely well tolerated. The nine-valent HPV vaccine is approved for 9- to 45-year-old males and females and has an FDA indication for prevention of cervical, vaginal, vulvar, and anal cancer and genital warts due to vaccine types. CROSS-PROTECTION OF HPV VACCINES Women who receive any of the available HPV vaccines produce neutralizing antibodies to virus types that are closely related to type 16 or 18. Analyses of data from clinical trials suggest that the HPV vaccines may offer limited crossprotection against nonvaccine virus types. Over short periods, the bivalent vaccine appears more efficacious against HPV types 31, 33, and 45 than the quadrivalent vaccine, but differences in study design make direct comparisons difficult if not impossible. In addition, in the bivalent vaccine trials, vaccine efficacy against persistent infections with HPV types 31 and 45 waned over time, whereas efficacy against persistent infection with HPV type 16 or 18 remained stable. These results suggest that cross-protection is likely to be shorter lived than efficacy against infection and disease caused by vaccine types. SINGLE-DOSE VACCINATION As a cost saving measure, the World Health Organization has recommended that 9- to 15-year-olds may be vaccinated with a single dose of an HPV vaccine. This strategy appears to yield similar antibody titers to a two-dose regimen, but the level and duration of protection against infection and disease are not fully understood. A single-dose strategy has not been recommended by the FDA or other regulatory agencies in the United States. RECOMMENDATIONS FOR HPV VACCINATION The most recent guide lines for HPV vaccination from the Advisory Committee on Immuni zation Practices (ACIP) are summarized below and provided in detail at https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html. No prevaccination testing of any kind is recommended to establish whether the HPV vaccine should be administered to an individual. The HPV vaccine should be administered, if possible, before exposure to HPV through sexual activity because the vaccines are preventa tive against specific HPV types and have no effect on preexisting, type-specific HPV infections. Either the bivalent (where available) or nine-valent HPV vaccines may be used. An individual can begin a vaccine series with one HPV vaccine and then complete the series with another. For those who have completed a vaccination series with the bivalent or quadrivalent vaccine, an additional full series (two or three doses, depending on age as indicated above) of vaccination with the nine-valent vaccine may be given, but there are no data to determine the effectiveness of this approach. For

children, adolescents, and adults (male and female) 9−26 years of age, the ACIP recommends HPV vaccination at age 11 or 12 years, although vaccination can be initiated at 9 years of age per FDA approval as above. “Catch-up” HPV vaccination is recommended for men and women through 26 years of age who are not adequately vaccinated. For adults (male and female) 27−45 years of age, catch-up HPV vaccination is not routinely recommended. Instead, the ACIP now recommends “shared clinical decision-making” (see below) regarding HPV vaccination for adults in this age range who are not adequately vaccinated. HPV vaccines are not licensed for use in adults older than 45 years of age. For women, cervical cancer screening should continue according to age-specific guidelines regardless of having received an HPV vaccine (see cervical cancer screening section below). SHARED CLINICAL DECISION-MAKING FOR ADULTS (MALES AND FEMALES) 27−45 YEARS OF AGE A discussion with adults 27−45 years of age should occur prior to routine recommendation of the HPV vaccine. HPV infection occurs soon after first sexual activity in most people, and vaccine effectiveness is therefore lower in older individuals due to prior infections. HPV exposure usually decreases among older age groups. Although HPV vaccination is safe for adults 27−45 years of age, the benefit to the population is likely to be minimal. However, some men and women who are not vaccinated may be at risk for acquisition of new HPV infections and could therefore benefit from HPV vaccination.

In considering HPV vaccination of adults 27−45 years of age, some key points emphasized by the ACIP that should be discussed include the following:

• HPV is a common sexually transmitted infection, and most HPV infections are asymptomatic and do not lead to clinical disease. • Most sexually active adults have been exposed to HPV, although not necessarily all of the HPV types targeted by vaccines. • Some adults are at risk for acquiring new HPV infections through sexual activity. For example, having a new sex partner is a risk factor for acquiring a new HPV infection. • Persons in a long-term, mutually monogamous sexual partnership are unlikely to acquire a new HPV infection. • Antibody testing cannot determine whether a person is immune or susceptible to a specific HPV type. • HPV vaccines are very effective in persons who have not been exposed to vaccine-type HPV before vaccination. • Vaccine effectiveness is likely to be lower among persons with mul tiple lifetime sex partners because these individuals have probably had previous infections with vaccine-type HPV. • HPV vaccines are prophylactic (i.e., they prevent new HPV infec tions). They have no utility in preventing established HPV infection from progressing to clinical disease, and they do not have a role in treatment of HPV-associated disease. RECOMMENDATIONS FOR HPV VACCINATION IN PEOPLE LIVING WITH HIV (PLWH) Guidelines for HPV vaccination of PLWH are summarized below and can be found in detail at https://hivinfo.nih.gov. HPV vaccines are safe in PLWH. Administration of HPV vaccines generates high levels of antibody against HPV types represented in vaccine, although antibody levels are generally lower than in those who are HIV-uninfected. In addition, immune responses appear stron ger among PLWH who have the highest CD4 counts and the lowest HIV viral loads. Studies also indicate that HPV vaccination induces an anamnestic response in PLWH. Regarding efficacy in protect ing against HPV-associated disease, one randomized, double-blind, clinical trial evaluated the efficacy of the quadrivalent HPV vaccine in adults with HIV infection older than 27 years in prevention of new anal HPV infections or improvement in high-grade dysplastic anal lesions. The trial did not show efficacy, but many study participants had HPV infection detected at baseline, prior to vaccination. CHAPTER 203 Human Papillomavirus Infections HPV vaccination is recommended (three doses) for girls and boys with HIV infection 11−26 years of age. Because

some individuals with HIV infection (similar to HIV-uninfected individuals) have had many sex partners prior to vaccination, HPV vaccination may be less benefi cial in these patients than in those with few or no lifetime sex partners. Current data do not strongly support vaccination for those PLWH older than 26 years. The public health benefit for HPV vaccination of PLWH in this age range is likely to be minimal. However, although many PLWH ages 27–45 years will not fully benefit from the vaccine, there may be situations that suggest the possibility of vaccine ben efit, and the same shared clinical decision-making (described above) between the provider and patient is recommended. ■ ■SCREENING FOR HPV-ASSOCIATED CANCER Once HPV infection occurs, prevention of HPV-associated disease relies on screening. At present, screening for cervical cancer is widely accepted as cost-effective in preventing cervical cancer. Anal screen ing is accepted for screening in high-risk groups, though no national guidelines exist for screening intervals or ages for initiation and ces sation of screening. In resource-rich countries, the primary method of cervical cancer screening is cytology via Pap smear. The American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines recommend initiation of cervical cancer screening at age 21, no mat ter the age of sexual debut. Women 21−29 years old should have a Pap smear every 3 years if their initial and subsequent Pap smears are normal. Although adolescent and young women often test HPV DNA positive, they are at very low risk of cervical cancer. Because the pres ence of HPV DNA does not correlate with the presence of high-grade

squamous intraepithelial neoplasia, co-testing (testing for HPV DNA at the time of Pap smear) is not recommended for women in this age group.

As a method of determining the need for colposcopy, HPV DNA co-testing is recommended for women 25−29 years of age in whom cytology detects abnormal squamous cells of undetermined signifi cance (ASCUS). Women 30−65 should have a Pap smear every 3 years if testing for HPV DNA is not performed. The screening interval for women in this age group can be extended to every 5 years if HPV DNA co-testing is performed and results are negative. HPV testing is not recommended for partners of women with HPV or for screening of conditions other than cervical cancer. The role of HPV DNA testing as a primary screen for cervical cancer is changing. In the United States, there are three commercially avail able assays (cobas HPV Test [Roche Diagnostics], the BD Onclarity HPV Assay [Becton, Dickinson and Company], and Alinity m HR HPV Assay (Abbott Molecular Diagnostics)) that are FDA approved for primary screening using HPV DNA testing. However, more assays may gain approval for usage as the feasibility and evidence for their use in various populations globally come to light. These tests can be used to detect HPV DNA in specimens obtained from the cervix without cervical cytology for women ≥25 years of age. A positive result for HPV type 16 or 18 has a high enough positive predictive value in the general population that these women should have colposcopy performed. If high-risk HPV types other than HPV 16 or HPV 18 are detected, then cytology can be obtained. The complete set of algorithms for appropri ate age-specific screening guidelines, HPV DNA testing, and the man agement of abnormal Pap smears are available through the ASCCP at http://asccp.org/guidelines. PART 5 Infectious Diseases For women ≤30 years of age who are infected with HIV, cervical cytology is the preferred method of cervical cancer screening and HPV DNA co-testing is not recommended. Cervical cancer screening should begin within 1 year of diagnosis of HIV infection, regardless of the mode of HIV transmission. If the first Pap smear is normal, then subsequent Pap smears should be performed annually until three negative tests are obtained. Cytology can then be obtained every 3 years. For women ≥30 years old, Pap testing is performed in the same manner as for younger

women. However, HPV DNA co-testing can be used in women of this age group. If cytology and HPV DNA co-testing are negative, the next exam can be performed in 3 years. Positive HPV DNA co-test results are treated in the same manner as in HIV-uninfected women. Women residing in developing countries with a lack of access to cervical screening programs have a higher rate of cervical cancer and a poorer cancer-specific survival. Approximately 75% of women liv ing in developed countries have been screened in the past 5 years, as opposed to ~5% of women living in developing countries. Economic and logistic obstacles likely impede routine cervical cancer screening for these populations. Many poor countries rely on an alternative method—visual inspection with acetic acid (VIA)—for cervical can cer screening. While some studies show a reduction in cervical cancer mortality in communities where VIA is widely utilized, other stud ies do not. In addition, the low specificity of VIA is problematic. As newer methods that use detection of oncogenic HPV DNA become available, even resource-limited countries may be able to replace VIA with such methods and achieve a reduction in cervical cancers as a result. There are no anal cancer screening guidelines endorsed by organiza tions such as the United States Preventative Services Task Force. The International Anal Neoplasia Society has published consensus guide lines regarding screening for anal cancer in patients at higher risk such as those with HIV. Current HIV treatment guidelines suggest that there may be a benefit to screening, but an effect on the associated morbidity and mortality of anal squamous cell cancer has not been consistently demonstrated. Although the most effective method of screening for anal cancer has not been determined, data published from a random ized controlled treatment trial noted a significant reduction in progres sion of high-grade precancerous lesions of the anus to anal cancer in those who received treatment. Further studies on optimal screening strategies for anal cancer are ongoing.

The incidence of HPV-associated head and neck cancers in the United States has overtaken the incidence of cervical cancer as of 2020, but there are no established guidelines for screening for HPV-associated head and neck cancers. However, HPV vaccination is likely to be effec tive for both anal and head and neck cancers associated with HPV. TREATMENT HPV-Associated Disease A variety of treatment modalities are available for various HPV infections, but none has been proven to eliminate HPV from tissue adjacent to the destroyed and infected tissue. Treatment efficacies are limited by frequent recurrences, presumably due to reinfection from an infected partner, reactivation of latent virus, or autoinoculation from nearby infected cells. The goals of treatment include prevention of viral transmission, eradication of premalig nant lesions, and reduction of symptoms. Therapies are generally successful in eliminating visible lesions and grossly diseased tissue. Different therapies are indicated for geni tal warts, vaginal and cervical disease, and perianal and anal disease. THERAPEUTIC OPTIONS Imiquimod Imiquimod (5 or 3.75% cream) is a patient-applied topical immunomodulatory agent thought to activate immune cells by binding to a Toll-like receptor that leads to an inflamma tory response. Imiquimod 5% cream is applied to genital warts at bedtime three times per week for up to 16 weeks. Warts are cleared in ~56% of patients, more often in women than in men; recurrence rates approach 13%. Local inflammatory side effects are com mon. Rates of clearance of genital warts are not as high with the 3.75% formulation as with the 5% preparation, but the duration of treatment is shorter (daily application required for a maximum of 8 weeks) and fewer local and systemic adverse reactions occur. Imiquimod should not be used to treat vaginal, cervical, or anal lesions. The safety of imiquimod during pregnancy has not been established. Interferon Recombinant interferon α is used for intralesional treatment of genital warts, including perianal lesions. The recom mended dosage is 1.0 × 106 IU of interferon into each lesion three times weekly for 3 weeks. Interferon therapy causes clearance of infected cells by immune-boosting effects. Adverse events include headache,

nausea, vomiting, fatigue, and myalgia. Interferon ther apy is costly and should be reserved for severe cases that do not respond to less expensive treatments. Interferon should not be used to treat vaginal, cervical, or anal lesions. Cryotherapy Cryotherapy (liquid nitrogen treatment) for HPVassociated lesions causes cellular death. Genital warts usually disap pear after two or three weekly sessions but often recur. Cryotherapy, which is nontoxic and is not associated with significant adverse reactions, can also be used for diseased cervical tissue. Local pain occurs frequently. Surgical Methods Exophytic lesions can be surgically removed after intradermal injection of 1% lidocaine. This treatment is well tolerated but can cause scarring and requires hemostasis. Genital warts can also be destroyed by electrocautery, in which no addi tional hemostasis is required. Laser Therapy Laser treatment affords destruction of exophytic lesions and other HPV-infected tissue while preserving normal tissue. Local anesthetics are generally adequate. Efficacy for genital lesions is at least equal to that of other therapies (60–90%), with low recurrence rates (5–10%). Complications include local pain, vagi nal discharge, periurethral swelling, and penile or vulvar swelling. Laser therapy has also been used successfully for cervical dysplasia and anal disease caused by HPV. Therapeutic Vaccines The innate and adaptive immune systems are altered in patients with HPV-associated cancers. Antitumor

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