Human Papillomavirus (HPV) (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations

- HIV-infected individuals should use latex condoms during every act of sexual intercourse to reduce the risk of exposure to sexually transmitted pathogens, including human papillomavirus (HPV) **(AII)**.
- Ideally, HPV vaccine should be administered before an individual becomes sexually active **(AIII)**.
- HPV vaccination is recommended in HIV-infected females and males aged 11 to 12 **(AIII)** and 13 to 26 **(BIII)** years. HPV vaccination also can be administered to HIV-infected males and females aged 9 to 10 years. The bivalent and quadrivalent vaccines are approved for females and the quadrivalent vaccine is approved for males.
- Sexually active female adolescents who are HIV-infected should have routine cervical cancer screening whether or not they have been vaccinated **(AIII)**.
- HIV-infected female adolescents who have initiated sexual intercourse should have cervical screening cytology (liquid-based or Pap smear) obtained twice at 6-month intervals during the first year after diagnosis of HIV infection, and if the results are normal, annually thereafter **(AII)**. A Pap smear should be performed within 1 year of onset of sexual activity, regardless of age or method of HIV transmission **(BIII)**.
- If the results of the Pap smear are abnormal, in general, care should be provided according to the Guidelines for Management of Women with Abnormal Cervical Cancer Screening Tests by the American Society for Colposcopy and Cervical Pathology (http://www.asccp.org/ConsensusGuidelines/tabid/7436/Default.aspx).
- HIV-infected adolescent females should be referred for colposcopy if they have any of the following: squamous intraepithelial lesion (SIL), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical squamous cells—cannot exclude a high grade intraepithelial lesion (ASC-H). For HIV-infected adolescent females with atypical squamous cells of undetermined significance (ASC-US), either immediate referral to colposcopy or repeat cytology in 6-12 months is recommended. If ASC-US or greater is found on repeat cytology, referral to colposcopy is warranted **(BIII)**. Use of HPV testing is not recommended for screening or for triage of HIV-infected women with abnormal cytology results or follow-up after treatment **(BIII)**.
- Because of the high rate of recurrence after treatment, conservative management of cervical intraepithelial neoplasia-1 (CIN1) and CIN2 with observation is the preferred method for HIV-infected adolescent females **(BIII)**.
- Because risk of recurrence of CIN and cervical cancer after conventional therapy is increased in HIV-infected females, patients should be carefully followed after treatment with frequent cytologic screening and colposcopic examination according to published guidelines **(AII)**.
- Genital warts should be treated per the 2010 Centers for Disease Control and Prevention STD treatment guidelines (located at http://www.cdc.gov/std/treatment/2010/)

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*

† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Epidemiology

The majority of human papillomaviruses (HPV) fall predominantly into the alpha HPV genus. Alpha HPV infects cutaneous and mucosal squamous epithelium. More than 100 distinct types of alpha HPV exist.[1] HPV can be detected on normal healthy mucosal and cutaneous surfaces but also is associated with warts and anogenital pre-cancers and cancers and oropharyngeal cancers in adults, and in rare cases, in adolescents and children. Certain types are found predominantly in cutaneous warts (such as HPV2) whereas other distinct

mucosal types are associated with anogenital and oropharyngeal cancers. The mucosal HPV types found in cancers are referred to as high-risk and those not associated with cancers are referred to as low-risk types. Of the approximately 40-plus genital (i.e., mucosal) HPV types, 12 types have been established as high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59), and 6 as probable high-risk (26, 53, 66, 68, 73, 82).[1] HPV16 alone accounts for 50% of all squamous cell (SC) cervical cancers and 80% to 90% of all SC anal cancers. Of the HPV-associated vulvar, vaginal, penile, and oropharyngeal cancers, HPV16 is attributed to 50% to 80% as well.[2-4]

Skin warts associated with HPV are common in children,[5-7] whereas mucosal warts, including anogenital[8,9] and oral warts, are less common.[10]

HPV-associated cutaneous warts are transmitted by close person-to-person contact that is facilitated by minor trauma to the skin. Skin warts are most commonly associated with cutaneous HPV types 1, 2, 3, 4, 27, and 57, and are associated with distinct wart histology. The estimated prevalence of skin warts in immunocompetent children varies by population from approximately 5% to 50%.[5-7] In comparison, children with compromised cellular immunity often have intense and widespread appearance of both cutaneous and mucosal warts. Unfortunately, no data are available on prevalence or incidence of skin warts in HIV-infected children.

HPV-associated anogenital warts are known to be transmitted by sexual contact, thereby raising the concern of sexual abuse when diagnosed in pre-pubertal children.[9,11] The prevalence of HPV-associated anogenital warts varies by population and risk factors, For example, varying prevalences of HPV-associated anogenital warts have been reported in children; 0% in non-abused pre-pubertal children,[8] 1.7/1000 in children referred to a tertiary care hospital[9] and 1.8% in children with suspected sexual abuse.[12] Several studies have shown that anogenital warts can be found in children with no evidence of sexual abuse, suggesting that transmission may occur through other means such as perinatally[13] or through other non-sexual means (e.g., autoinoculation or transmission from the hands or mouth of a caretaker).[14-16] HPV6 and 11 are the most common types detected in anogenital warts in children.[17] In one study of children with anogenital warts, 24% of children had an adult family member with anogenital warts, 63% had a mother with cervical intraepithelial neoplasia (CIN), and 48% had a family member with extra-genital warts,[18] suggesting non-sexual transmission as the route of infection.[19] Rarely, cutaneous HPV types also have been associated with anogenital warts in children.[20] Oral papillomas also have been described in children as well as sexually active adolescents and are commonly associated with HPV6 and 11. Juvenile Onset Recurrent Respiratory Papillomatosis (JORRP), which is also associated with HPV6 and 11, can be life-threatening due to the ability of the lesions to cause airway obstruction. Incidence of JORRP in the United States is around 1.7 to 4.3 per 100,000.

Detection of HPV DNA in normal tissue of infants has been documented, suggesting that perinatal transmission also can occur. Rates of HPV DNA detected in newborns vary significantly (0%–70%), and when found in the infant, concordance between the mother and infant also is quite variable (<1%–100%).[21-23] Studies completed before 2000 tended to have higher rates of detection, whereas more recent studies find low rates of HPV DNA detected in infants (<5%). A systematic quantitative review of maternal-neonatal transmission concluded that pooled mother-to-child HPV transmission was around 6.5%.[21] Several authors have suggested that the rate of HPV detection in infants depends on the rate found in pregnant mothers.[22,24] Risks of DNA detection in newborns include mother's HPV status at delivery and presence of anogenital lesions (i.e., condyloma or squamous intraepithelial lesion [SIL]) in the mother.[22,23] Recent studies have concluded that pregnancy itself, even in HIV-infected women, is not associated with increased vulnerability to HPV.[25]

In a recent study, 19.7% of infants born to HPV-infected mothers and 16.9% of infants born to mothers who were HPV-negative at delivery were found to be HPV-positive in their orogenital area at some time during a 14-month follow-up period, suggesting that vertical transmission is not the sole source of oral or genital HPV infection in infants.[22] Although maternal history of condyloma at time of delivery has been a well-described risk factor for appearance of genital condyloma in infants months later, the risk remains quite low, with estimates of 7 per 1,000 births with a maternal history of genital warts.[26] In a parent-child study in Finland,[27] the cumulative detection rates for high-risk HPV from the child's genital and oral samples were 36% and 42%, respectively.[28] However, persistence of HPV was less common, with persistent oral HPV in 10% of

infants and persistent genital HPV in 1.5% of infants. Together, these data show that while oral and genital perinatal transmission can occur, persistence is unusual when infection is acquired (whether through vertical or horizontal transmission).

Genital HPV is most commonly a result of sexual transmission. Young age at first sexual intercourse and a higher number of recent sex partners are strong risk factors for HPV in both women and men.[29-34] Prevalence of HPV is common in sexually active adolescent girls, with prevalence of 12% to 64%, compared with 2% to 7% in women aged >35 years.[32,35-37] Cervical HPV is acquired shortly after onset of sexual activity, with 50% cumulative exposure within 3 years,[29,30] even among young women with one sex partner.[38] Recent data on young men suggest similarly high rates of genital HPV acquisition associated with number of sexual partners.[39] Rates of HPV are higher in HIV-infected adolescents and adult women than in HIV-uninfected women.[40-42] As with HPV, CIN and condyloma also are more common in HIV-infected women than uninfected women.[43-47]

Although the incidence of anogenital HPV infection in sexually active youth is high, longitudinal studies have demonstrated that 80% to 90% of infections in HIV-uninfected youth are transient, and spontaneously regress.[48,49] Repeated infections with new types are common,[49] but whether repeat detection of same-HPV-type infections result from new exposures or from reactivation of latent infection is unknown.[50] Rates of clearance of genital HPV infection are even higher in men.[39] Overall prevalence of HPV remains above 50% in men across all age groups, suggesting that repeated infections are even more common in men than in women.[51] A risk for HPV in the anus in women is associated with anal intercourse.[52,53] One study also showed that anal HPV acquisition was associated with cervical HPV infection and was quite common even without reported anal intercourse, suggesting that other sexual and non-sexual routes of anal acquisition are possible.[53]

The higher prevalence of HPV infections in HIV-infected populations may result partly from increased HPV persistence in these patients. In one study of adolescents with HIV, only 50% cleared their HPV infections.[54] Detection of anal HPV also is higher in HIV-infected youth.[55] Receptive anal sex is a risk factor for anal HPV in HIV-infected and HIV-uninfected men;[56] the association between anal HPV infection and anal sex is not as clear for women.[55,57] In studies of HIV-infected and -uninfected women, anal HPV infection is equal to if not more prevalent than cervical infection.[53,58]

Persistent infection with high-risk HPV types is associated with increased risk of CIN and cervical and vulvovaginal carcinoma in women and of anal intraepithelial neoplasia (AIN) and anal carcinoma in both women and men. Rates of HPV-associated cancers including cervical, vulvar, vaginal, penile, anal (men and women), and oropharyngeal are higher in HIV-infected individuals[59-61] and believed to result predominantly from the increased risk of persistent infection in this group. The rates are highest in HIV-infected young people.[59] Adolescent girls, whether HIV-infected or -uninfected, differ biologically from adult women (e.g., increased areas of cervical squamous metaplasia in adolescents, resulting in an increased susceptibility to either persistent infection or disease).[40,62]

Even though combination antiretroviral therapy (cART) has dramatically altered HIV's natural history, its impact on HPV and HPV-associated neoplasia is less clear. Several studies have shown that HPV prevalence and rates of CIN and AIN have not been reduced with cART,[54,63,64] in contrast to rates of Kaposi sarcoma, which have fallen dramatically since the advent of cART. Current data suggest that cervical cancer rates have decreased in most racial/ethnic groups, while anal cancer rates have increased in HIV-infected individuals.[65]

Other risks associated with increasing rates of cervical cancer include lack of cervical cancer screening, prolonged use of hormonal contraception, parity, smoking, and immunocompromising conditions (other than HIV).[31] A recent study of perinatally infected adolescents showed that 30% of HIV-infected girls had an abnormal (atypical squamous cells of undetermined significance [ASC-US] or greater) Pap smear.[66] The mean age at the time of the first Pap smear was 16.7 years (range 13–23 years). The observational study also noted that 23 cases of condyloma were reported in those younger than age 13. In a small study of Brazilian infants, HIV in the mother was noted to be a risk factor for neonatal transmission.[24] These data suggest that perinatally infected children may be more vulnerable to maternal transmission of HPV, because of higher rates of HPV in this group, and higher rates of HPV persistence in the neonatal and infant period due to immunosuppression.

Clinical Manifestations

Genital, Anal, Oral and Skin Warts

Genital HPV types cause hyperplastic, papillomatous, and verrucous squamous epithelial lesions (warts) on skin and mucus membranes, including anal, genital, oral, nasal, conjunctiva, gastrointestinal, bladder, and respiratory tract mucosa. Lesions in the genital area are often referred to as condyloma accuminata. Warts can be single or present with multiple lesions and often appear as papules, flat, smooth or pedunculated lesions. Common sites for skin warts are the hand, elbows, knees, and feet. JORRP can present with hoarseness and difficulty breathing.

Precancerous and Cancerous Lesions

Genital lesions associated with HPV include high grade CIN; vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), and AIN. Most intraepithelial neoplasias are asymptomatic. Cancers associated with high-risk HPV types include cervical, vulvar, vaginal, penile, anal, and oropharyngeal, specifically at the base of the tongue and tonsils. Cancers are often asymptomatic but also can be associated with bleeding, pain or a palpable mass.

Diagnosis

Genital, Anal, Oral and Skin Warts

Most cutaneous and anogenital warts can be diagnosed by visual inspection. A speculum examination may be required for cervical and vaginal lesions and anoscopy for intra-anal lesions. If the lesions do not respond to standard therapy or the warts are pigmented, indurated, fixed, or ulcerated, biopsy may be needed.

Patients in whom cancer or JORRP is suspected should be referred to an expert for diagnosis and management.

Intraepithelial and Squamous Cell Cancers

The same cytology and colposcopic techniques used to detect CIN in HIV-uninfected patients should be used in HIV-infected patients. Cytology is a screening test for cervical cancer (see Prevention section). However, histology remains the gold standard for confirming CIN and invasive cancers. In sexually active individuals, the entire genitalia and anal canal should be inspected carefully for visual signs of warts, intraepithelial neoplasia or invasive cancers. Vaginal, vulvar, and anal cancers often can be palpated by digital examination of the vaginal, vulvar, and intra-anal regions. Diagnosis is by histology; CIN, AIN, VaIN, VIN, and oral cancer are recognized through visual inspection, which includes colposcopy and high-resolution anoscopy (HRA), and biopsy to confirm diagnosis.

Role of HPV Testing

HPV DNA can be detected using several platforms.[67] HPV tests available can detect from 2 to 13 to 14 oncogenic HPV types in clinical specimens. Currently, data are insufficient for use of HPV testing in triage of HIV-infected women with abnormal cytology results or for follow-up after treatment **(BIII)**, and it is not recommended for primary screening for any women younger than age 30. HPV testing also is not helpful in diagnosing or managing visible genital, skin or oral warts. HPV testing is not recommended in any circumstance for adolescent girls (aged <20 years),[68] regardless of whether they are HIV-infected or HIV-uninfected, because of the high rates of HPV infection.

Prevention Recommendations

Preventing Exposure

HIV-infected individuals should use latex condoms during every act of sexual intercourse to reduce the risk of exposure to (or transmission of) sexually transmitted pathogens **(AII)**. Condom use has been shown to

reduce HPV genital acquisition, reduce risk of genital warts, and enhance clearance of CIN.[33,69,70] This is true in both HIV-infected men and women.[71] In all circumstances where a male condom cannot be used properly, the use of a female condom may be protective for vaginal intercourse **(AII)**, but may not be protective for anal intercourse involving either women **(BIII)** or men who have sex with men **(BIII)**.[72,73]

HPV Vaccine

The quadrivalent and bivalent vaccines have been shown to prevent HPV16 and 18 infections and associated precancers in females and the quadrivalent has been shown to prevent HPV16 and 18 infections and precancers in males. The quadrivalent vaccine also protects against HPV6 and 11 infections and associated genital warts in females and males.[74-77] Because the HPV vaccine prevents infection and is not therapeutic, it ideally should be administered before potential exposure to HPV through sexual contact **(AIII)**. Data from clinical trials[75] of both vaccines showed that if previous exposure to the vaccine HPV types was documented, no efficacy was noted for that type, underscoring the fact that the vaccine is not therapeutic.

A randomized clinical trial of the quadrivalent HPV vaccine in the United States found the vaccine to be safe and immunogenic in HIV-infected children aged 8 to 11 years.[78] Serum antibodies to HPV6 and 18 were 30% to 50% lower than in historic age-matched immunocompetent controls. In addition, at 18 months after the third dose of vaccine, 94% to 99% had antibody to HPV6, 11, and 16, however, only 76% had antibody to HPV18. This group was also given a fourth dose which demonstrated an excellent amnestic response for all the vaccine associated HPV types.[79] The clinical significance of this observation is unknown. Ongoing studies will continue to evaluate the efficacy and duration of immune response in HIV-infected boys and girls. Although no studies in HIV-infected adolescents and adult women have yet been published, a study in HIV-infected men found the vaccine to be safe and immunogenic.[80]

Data on prior exposure to vaccine types in HIV-positive individuals aged 13 to 26 years are insufficient to determine the proportion that would benefit from vaccination.

HPV vaccination in HIV-infected youth is recommended **(AIII)**. Either bivalent or quadrivalent HPV vaccine offers protection against the two most common types that are associated with HPV-associated genital cancers. Quadrivalent vaccine also offers protection against the two most common types that cause genital warts. Either the bivalent or quadrivalent HPV vaccine is recommended for routine vaccination of HIV-infected females aged 11 to 12 years; quadrivalent HPV vaccine is recommended for routine vaccination of HIV-infected males aged 11 to 12 years.

The first dose of the HPV vaccine series should be administered to males and females aged 11 to 12 years, but can be administered as early as age 9 years. The second dose should be administered 1 to 2 months after the first dose, and the third dose should be administered 6 months after the first dose. HIV-infected adolescents aged 13 to 26 years who have not been previously vaccinated or have not completed the vaccine series should be vaccinated (see http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6050a3.htm) **(AIII)**.

Preventing Disease

Circumcision

There is evidence that circumcision reduces the rates of oncogenic HPV infection of the penis,[81-85] and is associated with lower risk of penile cancer[86,87] and cervical cancer in sexual partners.[88] Because other studies suggest no benefit,[89] evidence is insufficient to recommend adult male circumcision solely for the purpose of reducing the risk of oncogenic HPV infection in HIV-infected men or their sex partners in the United States, or infant male circumcision solely for the purpose of reducing the future risk of oncogenic HPV infection before or after they initiate sex.

Preventing Cervical Cancer

HIV-infected adolescents and women who have initiated sexual intercourse should have cervical screening cytology (liquid-based or Pap smear) obtained twice at 6-month intervals during the first year after diagnosis of

HIV infection, and if the results are normal, annually thereafter **(AII)**. Because of the reportedly high rate of progression of abnormal cytology in HIV-infected adolescents[46] and young women who were infected through sexual intercourse, providers should consider screening within 1 year of onset of sexual activity, regardless of age or method of HIV acquisition **(BIII)**. Although no similar prospective data are available for perinatally infected adolescents, Brogly et al[66] reported that 30% of perinatally infected adolescents had an abnormality (ASCUS or greater) on their first Pap smear. HIV-infected adolescents and women who have become sexually active, whether vaccinated or not, should continue screening annually throughout their lives **(BIII)**. Evidence is insufficient to recommend cervical cancer screening in HIV-infected girls who are not sexually active.

If Pap smear results are abnormal, care should be provided according to the Guidelines for Management of Women with Abnormal Cervical Cancer Screening Tests by American Society for Colposcopy and Cervical Pathology.[68] Exceptions include the role of HPV testing in women age 21 and older (see section HPV Testing above). It is recommended that triage be done in HIV-infected adolescents similar to that in adult women, in that any SIL, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or atypical squamous cells cannot exclude a high-grade lesion (ASC-H) should be referred for colposcopy **(BIII)**. For ASC-US, either immediate referral to colposcopy or repeat cytology in 6 to 12 months is recommended. Some clinicians may opt for colposcopy in HIV-infected adolescents/women. If ASC-US or greater is found on repeat cytology, referral to colposcopy is warranted.

Preventing Vaginal and Vulvar Cancer

No routine screening for vaginal or vulvar cancer is recommended for HIV-infected children and adolescents. Women with a history of high-grade CIN or invasive cervical cancer are at increased risk of vulvar and vaginal cancer and should be referred to a specialist **(AIII)**.

Preventing Anal Cancer

At this time, no national recommendations exist for routine screening for anal cancer; some specialists recommend anal cytologic screening for HIV-seropositive men and women **(CIII)**.[69] An annual digital anal examination may be useful to detect on palpation masses that could be anal cancer **(BIII)**.[90] If anal cytology is performed and indicates ASC-US, ASC-H, LSIL, or HSIL, then it should be followed by HRA **(BIII)**. Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer **(BIII)** (see section on treatment for details of treatment of AIN).

Treatment Recommendations

Treating Disease

Genital Warts

Multiple treatments for HPV-associated skin and external genital lesions exist, but no one treatment is ideal for all patients or all lesions **(CIII)**.[91] Treatment can induce wart-free periods, but the underlying viral infection can persist, resulting in recurrence. Treatment modalities for external genital warts are the same for HIV-infected and -uninfected populations. Guidelines for the treatment of warts found in the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines, 2010, should be followed.[92] Individuals who are immunosuppressed because of HIV may have larger or more numerous warts, and may not respond as well as immunocompetent individuals to therapy for genital warts. Recurrences after therapy also are an issue for these patients.[92-95] Topical treatments may be ineffective in patients with large or extensive lesions. Self-applied therapies include podofilox (0.5%) solution or gel, imiquimod (5%) cream, and sinecatechin ointment. Provider-applied agents include trichloroacetic or bichloroacetic acid (TCA; BCA) (80%–90% aqueous solution).

Other treatments include intralesional interferon-alfa (IFN-α) or 5-fluorouracil [5-FU]/epinephrine gel implant, and cidofovir topical gel (1%). Cidofovir gel (1%) is a topical preparation that has been evaluated in a limited number of adults for treatment of anogenital HPV infection **(CIII)**. Topical cidofovir can be

absorbed systemically and associated with renal toxicity.[96] Injectable therapy (such as with IFN-α or 5-FU/epinephrine gel implant) should be offered in only severe recalcitrant cases because of inconvenient routes of administration, frequent office visits, and a high frequency of systemic adverse effects.

Lesions can be removed by cryotherapy or surgery **(BIII)**. Cryotherapy (application of liquid nitrogen or dry ice) must be applied until each lesion is thoroughly frozen. Treatment can be repeated every 1 to 2 weeks up to 4 times. The major toxicity is local pain. Adequate local pain management is essential for all caustic treatments. Topical anesthetics are favored. Lesions can be removed surgically by tangential scissor, tangential shave excision, curettage, or electrosurgery.

Limited data are available on treatment of oral warts in HIV-infected patients. Limited lesions can be treated with provider-applied therapies such as TCA or BCA or surgical excision. Extensive lesions should be referred to an expert.[97]

Treatment of Histologically Confirmed CIN

HIV-infected female adolescents should be evaluated by a clinician with experience in colposcopy and treatment of cervical cancer precursors, and managed according to The American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.[68] Not only is progression of lesions more common in HIV-infected women, recurrence is also more common, thus close observation as outlined in the CDC Sexually Transmitted Diseases Treatment Guidelines, 2010, should be considered for management of CIN1 and 2. Follow-up with annual cytologic assessment is recommended for adolescents with CIN1 **(AII)**.[68] At the 12-month follow-up, only adolescents with HSIL or greater on repeat cytology should be referred back to colposcopy. At the 24-month follow-up, those with an ASCUS or greater result should be referred back to colposcopy **(AII)**.

For adolescent girls and young women with a histologic diagnosis of CIN2 or 3 not otherwise specified or cytologic diagnosis of HSIL, either treatment or observation for up to 24 months using both colposcopy and cytology at 6-month intervals is acceptable, provided colposcopy is satisfactory **(BIII)**.[68] When a histologic diagnosis of CIN2 is specified, observation is preferred, but treatment is acceptable. If compliance with follow-up is a concern, then treatment may be preferable for CIN2. When CIN3 is histologically diagnosed or when colposcopy is unsatisfactory, treatment is recommended **(BIII)**.

If the colposcopic appearance of the lesion worsens or if HSIL cytology or a high-grade colposcopic lesion persists for 1 year, repeat biopsy is recommended **(BIII)**. After 2 consecutive Negative for Intraepithelial Lesion or Malignancy results, adolescents and young women with normal colposcopy can return to routine cytologic screening **(BII)**. Treatment is recommended if CIN3 is subsequently identified or if CIN2 or 3 persists for 24 months **(BII)**.

Persistent CIN1, 2, and 3 lesions in HIV-infected women should be treated as in HIV-uninfected women.[68] Conventional therapies used to treat CIN2 or 3 include cryotherapy, laser therapy, cone biopsy, and a loop electrosurgical excision procedure (LEEP). Excisional methods are recommended for women with abnormal colposcopy and for women with recurrent disease **(AII)**. Recurrence rates of 40% to 60% after treatment have been reported in HIV-infected women undergoing these procedures.[98-100] Management of invasive cervical cancer should follow the National Comprehensive Cancer Network (NCCN) guidelines (http://www.nccn.org).

Treatment of VIN and Vulvar Cancer and of VaIN and Vaginal Cancer

Treatment of VIN/VaIN should be made in consultation with a specialist. Low-grade VIN/VaIN (VIN 1/VAIN 1) can be observed or managed as per recommendations for vulvovaginal warts. Various treatment modalities for VIN are available, including TCA, local excision, laser vaporization or ablation, and imiquimod therapy. Treatment options for VaIN include topical 5-FU, laser vaporization with a CO_2 laser, and excisional procedures with electrosurgical loops or a scalpel excision. Fluorouracil cream and ointments should not be used in pregnant women. Management of invasive vulvar or vaginal cancer should follow the NCCN guidelines (http://www.nccn.org).

Treatment of AIN

There are no adequate randomized, controlled, therapeutic trials reported for the treatment of AIN. Treatment decisions are based on size, location, and severity of histology. Several different treatments have been described in small open-label studies, including topical 5-FU or imiquimod, infrared coagulation, laser therapy, and surgical excision.[101-104] These data do not indicate that treatment for HIV-infected women with AIN should be modified for patients receiving cART nor is there evidence indicating that cART should be instituted or modified for the purpose of treating AIN.

Treatment of HPV-associated disease at other sites, including oral and penile lesions, does not differ in HIV-infected versus uninfected men and women.

Role of Antiretroviral Therapy

Severe immunosuppression is associated with greater HPV-associated morbidity and mortality. However, studies show conflicting findings in reducing risk of HPV-related cervical and anal HPV disease, therefore, intraepithelial neoplasia by itself is not an indication for initiating cART.

Monitoring of Adverse Events (Including IRIS)

Monitoring for toxicity and recurrences is required during and after treatment of genital warts. The major toxicity of podofilox, imiquimod, and sinecatechin ointment is inflammation at the application site. The major toxicity of cryotherapy is local pain. The major toxicities of surgical treatment for genital warts are local pain, bleeding, and secondary infection. The major toxicities associated with acid cauterization are local pain and irritation or ulceration of adjacent normal skin. Intralesional IFN-α can be associated with systemic toxicities of IFN-α, including fever, fatigue, myalgia, malaise, depression, and other influenza-like symptoms. Infrared coagulation may lead to bleeding and abscess formation. Scarring can occur with any of the above treatment modalities. Topical cidofovir may result in systemic absorption and be associated with renal toxicity.[96]

Secondary infections are not uncommon if ulcerations occur, and close monitoring post-treatment for treatment-related toxicity is warranted. Treatment of CIN with ablative and excisional modalities can be associated with several adverse events such as pain and discomfort, intraoperative hemorrhage, post-operative hemorrhage, infection, and cervical stenosis. Treatment of AIN is associated with adverse events, including ulcerations, abscesses, fissures, and fistulas.

An immune reconstitution-like syndrome related to HPV-associated oral warts in HIV-infected adults has been observed in which occurrence of oral warts was associated with decreased HIV RNA levels with cART.[105] Immune reconstitution in response to viral load reduction may result in a return of marked inflammatory responses against latent oral HPV infection. Some studies,[105,106] but not others,[107] have reported an increase in oral warts following cART initiation.

Preventing Recurrence

Monitoring after therapy for cervical disease should follow the ASCCP guidelines.[108] No recommendations exist for preventing recurrence of external genital warts. Patients should be monitored with cytologic screening according to published guidelines and, when indicated, colposcopic examination for recurrent lesions **(AI)**.[90,109]

Managing Treatment Failure

Treatment failure is defined as the persistence or recurrence of lesions after appropriate therapy. For persistent or recurrent genital warts, re-treatment with any of the modalities previously described should be considered, preferably with an alternative modality to the one that previously failed **(AIII)**. Genital warts often require more than one course of treatment. Recalcitrant warts should be managed by experienced clinicians and referred for excisional therapy. Recurrence of CIN may require additional treatments (e.g., LEEP, laser). Excisional therapy is recommended for recurrent lesions. Recurrent cytologic and histologic abnormalities after therapy for CIN should be managed according to the ASCCP guidelines.[68] There is no consensus on the treatment of biopsy-

proven recurrent VIN, VaIN or AIN. Risk of recurrence of CIN and cervical cancer after conventional therapy is increased in HIV-infected women, and patients should be carefully followed after treatment with frequent cytologic screening and colposcopic examination according to published guidelines **(AII)**.[99,110]

Discontinuing Secondary Prophylaxis

Not applicable.

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Dosing Recommendations for Prevention and Treatment of Human Papillomavirus (HPV)

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	HPV vaccine	N/A	See Figure 2 for detailed vaccine recommendations.
Secondary Prophylaxis	N/A	N/A	N/A
Treatment	• Podofilox solution/gel (0.5%) applied topically BID for 3 consecutive days a week up to 4 weeks (patient applied). Withhold treatment for 4 days and repeat the cycle weekly up to 4 times **(BIII)** • Imiquimod cream (5%) applied topically at night and washed off in the morning for 3 non-consecutive nights a week for up to 16 weeks (patient applied) **(BII)** • TCA or BCA (80%–90%) applied topically weekly for up to 3 to 6 weeks (provider applied) **(BIII)** • Podophyllin resin (10%–25% suspension in tincture of benzoin) applied topically and washed off several hours later, repeated weekly for 3 to 6 weeks (provider applied) **(CIII)** • Cryotherapy with liquid nitrogen or cryoprobe applied every 1–2 weeks **(BIII)** • Surgical removal either by tangential excision, tangential shave excision, curettage, or electrosurgery	• Intralesional IFN-α is generally not recommended because of high cost, difficult administration, and potential for systemic side effects **(CIII)** • Cidofovir topical gel (1%) is an experimental therapy studied in HIV-infected adults that is commercially available through compounding pharmacies and has very limited use in children; systemic absorption can occur **(CIII)**. • 5-FU/epinephrine gel implant should be offered in only severe recalcitrant cases because of inconvenient routes of administration, frequent office visits, and a high frequency of systemic adverse effects.	Adequate topical anesthetics to the genital area should be given before caustic modalities are applied. Sexual contact should be limited while solutions or creams are on the skin. Although sinecatechins (15% ointment) applied TID up to 16 weeks is recommended in immunocompetent individuals, data are insufficient on safety and efficacy in HIV-infected individuals. cART has not been consistently associated with reduced risk of HPV-related cervical abnormalities in HIV-infected women. Laryngeal papillomatosis generally requires referral to a pediatric otolaryngologist. Treatment is directed at maintaining the airway, rather than removing all disease. For women who have exophytic cervical warts, a biopsy to exclude HSIL must be performed before treatment. Liquid nitrogen or TCA/BCA is recommended for vaginal warts. Use of a cryoprobe in the vagina is not recommended. Cryotherapy with liquid nitrogen or podophyllin resin (10%–25%) is recommended for urethral meatal warts. Cryotherapy with liquid nitrogen or TCA/BCA or surgical removal is recommended for anal warts. Abnormal Pap smear cytology should be referred to colposcopy for diagnosis and management.

Key to Acronyms: 5-FU = 5-fluorouracil; BCA = bichloroacetic acid; BID = twice daily; cART = combination antiretroviral therapy; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; IFN-α = interferon alfa; TCA = trichloroacetic acid; TID = three times daily