

# Human Papillomavirus Disease

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## Epidemiology

Human papillomavirus (HPV) infection is the major risk factor for development of cervical cancer,<sup>1,2</sup> the fourth most common cancer in women worldwide.<sup>3,4</sup> Nearly all cervical cancers test positive for HPV genetic sequences,<sup>5-7</sup> most notably the E6 and E7 oncogenes,<sup>8-10</sup> which are thought to play a major role in immortalization of cervical epithelial cells.<sup>11</sup> Cervical infection with HPV is common and occurs primarily through sexual transmission.<sup>12-16</sup> Penetrative sexual intercourse is not strictly necessary for HPV transmission,<sup>17</sup> but it is the primary risk factor for HPV infection, and HPV prevalence is low in young women who report only nonpenetrative sexual contact.<sup>17,18</sup> The vast majority of cervical HPV infections resolve or become latent and undetectable, but in a subset of women, infection persists.<sup>12,19,20</sup> Persistence of oncogenic HPV infection is a necessary step in HPV-related cervical tumorigenesis,<sup>1,21,22</sup> although it appears insufficient for final cell transformation.<sup>11</sup> At least 12 HPV types are considered oncogenic, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.<sup>22-24</sup> HPV68 is considered “probably oncogenic,” and several other HPV types are considered “possibly oncogenic.” HPV16 alone, though, accounts for approximately 50% of cervical cancers in the general population and HPV18 for another 10% to 15%. The other oncogenic HPV types each individually account for fewer than 5% of tumors. HPV types 6 and 11 cause 90% of genital warts, but in general are not considered oncogenic.<sup>22-24</sup>

In the United States and Western Europe, women with HIV (WWH) have significantly higher rates of cervical cancer than women in the general population,<sup>25-31</sup> and recent cohort data show a direct relationship between low CD4 T lymphocyte (CD4) cell count and cervical cancer risk.<sup>32-34</sup> In Africa, the data are more limited,<sup>35</sup> but a prospective registry-based study found elevated risk of cervical cancer<sup>36,37</sup> as well as anal, vulvar, and penile cancer (each of which increased in incidence among people with HIV [PWH] between 2003 and 2015).<sup>37</sup> HIV infection and low CD4 cell count also have been associated consistently and strongly with HPV infection itself and with precancerous cervical lesions—including low-grade cervical intraepithelial neoplasia (CIN)—and the precursor to cervical cancer, CIN 3.<sup>38-50</sup>

Higher rates of HPV infection and CIN also were reported in HPV-unvaccinated adolescents with HIV, regardless of whether HIV was acquired vertically or horizontally.<sup>39,51,52</sup> For example, Brogly and colleagues reported that 30% of female adolescents with perinatal HIV infection had an abnormality (e.g., atypical squamous cells of uncertain significance [ASC-US] or greater) on their first Pap test; genital warts also were common in this group, with a cumulative rate of 12% by age 19 years.<sup>52,53</sup> However, few data exist regarding HPV vaccine efficacy or effectiveness in male or female adolescents or adults with HIV.<sup>54</sup> A recent paper shows the qHPV vaccine is effective in young men who have sex with men (MSM) with HIV to prevent anal squamous intraepithelial lesions associated with qHPV vaccine types among those naive to those types prior to vaccination.<sup>55</sup>

Other cancers caused by HPV include most anal cancers and a subset of tumors of the vulva, vagina, penis, oral cavity, and oropharynx.<sup>1,23,56-59</sup> HPV16 is the type present in most HPV-positive noncervical cancers.<sup>1,23,56,60,61</sup> PWH have a significantly elevated incidence of each of these HPV-

related tumors relative to the general population,<sup>25,62-64</sup> and CD4 cell count has been associated with the risk of anal cancer.<sup>32,65</sup> Furthermore, high-grade anal intraepithelial neoplasia (AIN), the likely anal cancer precursor lesion, is more common in adults and adolescents who are HIV seropositive than in those who are HIV seronegative,<sup>66-68</sup> as are anal and genital warts, and in women, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).<sup>69-71</sup> In the general U.S. population, HPV also causes approximately 70% of oropharyngeal cancers (OPC).<sup>72,73</sup> HPV16 causes 84% of HPV-associated OPC, and the HPV types contained in the nonavalent HPV vaccine cause approximately 94%.<sup>74</sup> HPV-associated OPC incidence is four- to fivefold higher in males than in females,<sup>75</sup> and two- to threefold higher among PWH.<sup>76-79</sup> Furthermore, PWH's high risk of HPV-associated cancers continues into older age (>50 years of age). This includes tumors of the cervix, anus, and oropharynx—an important finding given the increasing longevity of PWH.<sup>80</sup>

During the era of combination antiretroviral therapy (cART) the incidence of HPV-associated cancers has remained elevated in PWH relative to the general population,<sup>64</sup> though the extent of this disparity has decreased for at least some of these tumors. A recent registry-based study, for example, reported a highly statistically significant downward trend in anal cancer incidence relative to the general population ( $P = 0.0001$ ) (i.e., a reduction in standardized incidence ratio [SIR] from approximately SIR ~40 in 1996 to SIR ~20 in 2012).<sup>64</sup> A possible (nonsignificant;  $P = 0.09$ ) decrease in cervical cancer from SIR ~5 in 1996 to SIR ~3 in 2012, as well as a nonsignificant decrease in oral cavity/pharyngeal cancer, was observed.<sup>81</sup> Other HPV-related tumors are less common, and reliable data regarding the trends in their incidence are limited. Nonetheless, low-grade vulvar lesions and genital warts were found to decrease with cART,<sup>69</sup> and several studies found decreased incident detection, persistence, and progression of HPV and CIN with cART use<sup>82</sup>; including one study that distinguished between adherent versus nonadherent or effective versus ineffective cART use (based on HIV RNA level).<sup>83</sup>

Cervical cancer screening and treatment of precancer are, in and of themselves, a major burden confronting WWH. Positive HPV screening tests are several-fold more common in WWH than in the general population, and as many as 25% to 35% of WWH have an abnormal Pap test (ASC-US+) at each clinical visit<sup>84</sup>; leading to frequent, often repeated colposcopy and biopsy. Furthermore, most colposcopies and biopsies find low-grade lesions rather than clinically relevant disease (e.g., precancer, cancer). Thus, methods to reduce the high burden of unnecessary colposcopy and biopsy in WWH by improving the specificity and positive predictive value of cervical cancer screening methods is of great importance, especially because generations of WWH are above the age to receive the HPV vaccine.

For anal cancer, a major unresolved question is whether or not to conduct screening. Anal cancer risk varies extensively between MSM with HIV and MSM without AIDS, as well as between MSM with HIV and WWH or men who do not have sex with men.<sup>85,86</sup> For example, a recent study based on HIV/AIDS registry and cancer registry data found that the 5-year risk (cumulative incidence) of anal cancer was 0.33% and 0.52% in MSM without and with AIDS, respectively, whereas the results were 0.04% and 0.10% for men who do not have sex with men, and 0.08% and 0.20% for women. As a point of reference, colorectal and breast cancer, two cancers for which screening is conducted, the 5-year cumulative incidence is 0.27% and 0.89%.<sup>30</sup> However, anal cancer may have higher mortality. An NIH-funded randomized clinical trial of anal cancer screening, the [ANCHOR Study](#), is underway.

Anogenital warts are also an important HPV-associated disease in PWH. These lesions are very common, and more likely to be persistent in PWH than the general population. Approximately 80%

to 90% of anogenital warts are caused by non-oncogenic HPV types 6 or 11.<sup>87</sup> In the United States from 2003 to 2006, the incidence of anogenital warts was 4.0 to 5.2/1,000 person-years in women (ages 20–24 years) and 3.0 to 3.6/1,000 person-years in men (ages 25–29 years).<sup>88</sup> From the [NHANES](#) database, the estimated prevalence of anogenital warts is 2.9% of men ages 18 to 59 years and 2.2% of men reported a history of anogenital warts,<sup>89</sup> with several-fold greater rates in PWH.<sup>69,89</sup> HPV types 6 and 11 also have been associated with conjunctival, nasal, oral, and laryngeal warts.

Data regarding outcomes following treatment of HPV-related cancers in PWH are limited and need to be interpreted accordingly. Cancer-specific survival following treatment of anal and oropharyngeal cancer was reported to be similar in PWH and the general population, whereas cervical cancer survival following treatment was reported to be worse in WWH.<sup>90,91</sup> Another study found that although response to initial therapy for invasive cervical cancer (e.g., radiation treatment) was similar in WWH and other patients, HIV was associated with high risk of relapse (hazard ratio [HR] = 3.6; 1.86–6.98) and higher cervical cancer mortality.<sup>92</sup> Data from the AIDS Malignancy Consortium showed that WWH on antiretroviral therapy with locally advanced cervical cancer in sub-Saharan Africa can complete routine cisplatin and radiation therapy and that one-year progression-free overall survival rates observed among women with high-risk advanced tumors were similar to reported studies of women without HIV with generally smaller tumors.<sup>93</sup>

## Clinical Manifestations

The principal clinical manifestations of mucosal HPV infection are genital, anal, and oral warts; CIN; VIN; VAIN; AIN; anogenital squamous cell cancers; and cervical adenocarcinomas. A subset of oropharyngeal cancers are also caused by HPV.<sup>94</sup>

Oral, genital (condyloma acuminata), and anal warts are usually flat, papular, or pedunculated growths on the mucosa or epithelium. The lesions may measure a few millimeters to 1 to 2 centimeters in diameter. Most warts are asymptomatic, but warts can be associated with itching or discomfort. In cases associated with more severe immunosuppression, marked enlargement may cause dyspareunia or dyschezia. Lesions of any size may cause cosmetic concerns.

Intraepithelial neoplasias (CIN, VIN, VAIN, and AIN) are often asymptomatic but may manifest with bleeding or itching. Related cancers also may be asymptomatic or may manifest with bleeding, pain, odor, or a visible/palpable mass. External lesions may be visible or palpable. Similarly, squamous cell cancers at these sites also can be asymptomatic or may manifest with bleeding, pain, or a visible/palpable mass.

## Diagnosis

### *Warts/Condyloma*

Diagnosis of genital and oral warts is made by visual inspection and can be confirmed by biopsy, although biopsy is needed only if the diagnosis is uncertain; the lesions do not respond to standard therapy; or warts are pigmented, indurated, fixed, bleeding, or ulcerated. No data support the use of HPV testing for screening, diagnosis, or management of visible genital/oral warts or oral HPV disease in PWH.<sup>95</sup>

## ***Cervical Neoplasia***

The same cytology (Pap test), and colposcopic techniques with biopsy are used to detect CIN among patients who are HIV seronegative and those who are HIV seropositive (see section on Preventing Disease). At the time of cytology screening, the genitalia and anal canal should be inspected carefully for visual signs of warts, intraepithelial neoplasia, or invasive cancer.

## ***Anal and Vulvar/Vaginal Neoplasia***

AIN, VAIN, and VIN are recognized through visual inspection, including high-resolution anoscopy, colposcopy, and biopsy as needed. A digital examination of the anal canal to feel for masses should be performed as part of routine evaluation.<sup>96</sup>

## ***Cervical Cancer Screening Recommendations***

In a recent report from the HIV/AIDS Cancer Match Study (2002–2016)—which included a population of 164,084 WWH (64% Black, 21.8% Hispanic, 12.7% White, and 1.1% other race)—552 cases of invasive cervical cancer (ICC) occurred in 1.16 million person-years of follow-up (rate = 47.7 per 100,000). By age group, the highest incidence rates occurred among 40- to 44-year-olds and 35- to 39-year-olds (rate = 66.1 and 64.5 per 100,000, respectively). Zero cases of ICC occurred among <25-year-old WWH during 69,900 person-years of follow-up (SIR=0; 95% CI 0,7.1). When compared to the general population, rates of cervical cancer were elevated significantly—3 to 4 times overall (95% CI, 3.13–3.70). Because the absolute incidence of ICC is exceedingly low among WWH under 25 years, it is recommended that cervical cancer screening start at age 21. The rationale for beginning screening at age 21 is to provide a 3- to 5-year window prior to age 25, when the risk of ICC in WWH exceeds that of the general population.<sup>97</sup>

Available HPV tests can detect up to 14 oncogenic HPV types in clinical specimens and are sensitive for the detection of cervical cancer precursors. Some commercially available HPV tests will specify whether the oncogenic HPV includes genotypes HPV16 or HPV16/18. The available tests for oncogenic HPV have been incorporated into the screening algorithms. **Note:** HPV testing is always for oncogenic HPV types only; there is no role in testing for non-oncogenic HPV.

Observational epidemiologic “bridging studies” in PWH have been instrumental in the decisions to adopt several cervical cancer screening guidelines that had been validated in large clinical trials in the general population. This included studies that supported the incorporation of cervical HPV testing for determining referral to colposcopy versus retesting in 1 year or during routine follow-up. For example, despite the very high prevalence of HPV in WWH, normal cytology with negative HPV co-testing had a strong negative predictive value, with low 3- to 5-year incidence of CIN2+ regardless of CD4 count.<sup>98,99</sup> Conversely, the risk of precancer was high in WWH who tested positive for oncogenic HPV despite a normal Pap and several-fold greater still if HPV16 was specifically detected.<sup>100</sup> Additional studies showed that oncogenic HPV testing had high sensitivity and negative predictive value in the triage of borderline Pap test results (i.e., ASC-US).<sup>101</sup>

Possible Pap test results include the following:

- Normal (negative for intraepithelial lesion or malignancy)
- LSIL (low-grade squamous intraepithelial lesion) or CIN1 (cervical intraepithelial neoplasia grade 1)

- HSIL (high-grade squamous intraepithelial lesion) or CIN2, 3 (cervical intraepithelial neoplasia grade 2, 3)
- ASC-US (atypical squamous cells of uncertain significance)
- ASC-H (atypical squamous cells, cannot rule out a high-grade lesion)
- AGC (atypical glandular cells)

## Women With HIV Aged <30 years

### *Screening*

The Pap test is the primary mode for cervical cancer screening for WWH <30 years of age. WWH ages 21 to 29 years should have a Pap test at the time of initial diagnosis with HIV. Provided the initial Pap test for a young (or newly diagnosed) woman with HIV is normal, the next Pap test should occur in 12 months (**BII**). If the results of three consecutive Pap tests are normal, follow-up Pap tests should be every 3 years (**BII**). Co-testing (Pap test and HPV test) is not recommended for WWH <30 years of age.

### *Abnormal Pap Test Results*

Colposcopy is recommended for HPV-positive ASC-US (**AII**). If reflex HPV testing is not performed on ASC-US results, then repeat cytology in 6 to 12 months is recommended (**AII**). For any result equal to or greater than ASC-US on repeat cytology, referral to colposcopy is recommended (**AII**).

For LSIL or worse (including ASC-H, AGC, and HSIL), referral to colposcopy is recommended.

### *Rationale*

Because of the relatively high HPV prevalence before age 30 years, HPV co-testing is not recommended for women in this age group.

## Women With HIV Aged ≥30 years

Cervical cancer screening in WWH should continue throughout a woman's lifetime (and not, as in the general population, end at 65 years of age). Either Pap testing only, or Pap testing and HPV co-testing is acceptable for screening.

### *Pap Testing Only*

If screening with Pap tests alone, WWH should have a Pap test at the time of HIV diagnosis (baseline), then every 12 months (**BII**). If the results of three consecutive Pap tests are normal, follow-up Pap tests should be every 3 years (**BII**).

### *Pap and HPV Co-Testing*

If co-testing with Pap and HPV is available, then co-testing can be done at the time of diagnosis or at age 30 years. (**BII**). Women who co-test negative (i.e., a normal Pap and negative HPV test) can

have their next cervical cancer screening in 3 years.

Those with a normal Pap test but a positive HPV test should have repeat co-testing in one year (unless genotype testing for HPV16 or HPV16/18 is positive). If either of the co-tests at one year is abnormal (i.e., abnormal cytology or positive HPV), referral to colposcopy is recommended.

If the initial HPV results identify HPV16 or HPV16/18, referral to colposcopy is recommended. If the HPV testing is positive, but the genotype specific testing for HPV16 or HPV16/18 is negative, then repeat co-testing in one year is recommended. If either of the co-tests at one year is abnormal (i.e., abnormal cytology or positive HPV), referral to colposcopy is recommended.

### ***Abnormal Pap Test Results***

For ASC-US Pap test, if reflex HPV testing is negative, a repeat Pap test in 6 to 12 months or repeat co-testing in 12 months is recommended. For any result equal to or greater than ASC-US on repeat cytology, referral to colposcopy is recommended (**AI**).

For ASC-US Pap test, if reflex HPV testing is positive, then referral to colposcopy is recommended. If HPV testing is not available, repeat cytology in 6 to 12 months is recommended (**AI**). For any result equal to or greater than ASC-US on repeat cytology, referral to colposcopy is recommended (**AI**).

For LSIL or worse (including ASC-H, AGC, and HSIL) referral to colposcopy is recommended (regardless of HPV result, if done).

### ***Rationale***

Current guidelines from both the American Cancer Society and the U.S. Preventive Services Task Force allow use of HPV co-testing with cytology. A negative HPV test predicts prolonged low risk of cancer. Cytology/HPV co-testing can allow a prolonged cervical cancer screening interval in WWH who are older than 29 years and have normal cervical cytology with concurrent negative HPV testing.

For women older than 65 years, it is recommended to continue cervical cancer screening because WWH are at higher risk for cervical cancer. However, clinicians should consider other factors, such as the life expectancy of the patient and the risk for developing cervical cancer at this age.

## **Preventing HPV Infection**

### ***HPV Vaccine***

Three FDA-approved HPV vaccines exist: bivalent, quadrivalent, and 9-valent. Currently, only the 9-valent vaccine (HPV viral-like particles 6, 11, 16, 18, 31, 33, 45, 52, and 58) is available in the United States. This vaccine has an FDA indication for prevention of cervical, vaginal, vulvar, anal cancer, genital warts, and oropharyngeal and other head and neck cancers<sup>102</sup> due to vaccine types based on randomized clinical trial (RCT) data; albeit, these studies were not conducted in PWH.<sup>103-105,106-109</sup> Although no efficacy data exist for the 9-valent HPV vaccine in men with HIV, clinical trials established the safety of the vaccine in young men aged 16 to 26 years and showed similar antibody levels as in young women without HIV aged 16 to 26 years in whom efficacy was

established.<sup>110,111</sup>

Although no clinical trials have been conducted to demonstrate HPV vaccine efficacy in prevention of oropharyngeal cancers, some evidence exists that the prevalence of oral vaccine-type HPV infections are reduced with vaccination.<sup>112,113</sup> One prospective trial of the quadrivalent HPV vaccine in PWH older than 27 years suggested efficacy for prevention of oral HPV infection.<sup>114</sup>

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with 9-valent HPV vaccine. The target age for vaccination is 11 to 12 years (**AIII**). Vaccination through age 26 years is recommended, but vaccine effectiveness is lower if vaccination occurs after onset of sexual activity (**BII**). The vaccine series can be started at age 9 years. Catch-up vaccination is recommended for all 13- to 26-year-olds who have not been vaccinated.<sup>115-117</sup> Shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated.

The 9-valent vaccine should be delivered through a series of three intramuscular injections over a 6-month period. The second and third doses should be given at 1 to 2 months and then 6 months after the first dose.<sup>115,116</sup> Although ACIP recommends a two-dose schedule for adolescents initiating the vaccine series at ages 9 to 14 years,<sup>118</sup> three doses of HPV vaccine (0, 1–2, and 6 months) are recommended for females and males with HIV or other immune suppression because their immune response to vaccination might be attenuated.

One randomized, double-blind, clinical trial evaluated the efficacy of the quadrivalent HPV vaccine in PWH older than 27 years.<sup>114</sup> The trial did not show efficacy for prevention of new anal HPV infections or improvement in anal HSIL outcomes in this population with high levels of prior and current HPV infection. This trial and several other studies have established the safety and immunogenicity of HPV vaccines<sup>119,120</sup> in a broad range of PWH.<sup>121</sup> Some studies have demonstrated lower antibody levels in PWH than in those who do not have HIV; however, the clinical significance of this observation is unknown.<sup>122-124</sup> Studies have shown that HPV vaccination induces an anamnestic response in children and adults with HIV.<sup>120,125,104</sup> Immune responses appear stronger among those with higher CD4 counts and suppressed HIV viral loads.<sup>121,126</sup>

A recent prospective observational cohort study of female youth who had received quadrivalent HPV vaccine showed unexpectedly high rates of abnormal cervical cytology occurred in 33 of 56 perinatally infected youth and only 1 of 7 of perinatally exposed uninfected youth, yielding incidence rates of 100 person-years of 15 (10.9 to 29.6) and 2.9 (0.4 to 22.3), respectively. The majority of the diagnoses were LSIL or less, and the genotypes associated with these abnormal cytology results were unknown.<sup>127</sup>

For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, many experts would give an additional full series (three doses) of vaccination with recombinant 9-valent vaccine, but no data exist to define who might benefit or how cost effective this approach might be (**CIII**). The additional five high-risk HPV types covered by the 9-valent vaccine were found in 4.2% to 18.3% of HPV-associated anogenital cancers in U.S. men and women, depending on the cancer's location.<sup>74</sup>

HPV vaccination is recommended for girls and boys with HIV aged 13 to 26 years (**AIII**). HPV vaccination prevents initial HPV infection and is ideally administered before sexual exposure to HPV. Because some PWH have had many sex partners prior to vaccination, HPV vaccination may be less beneficial in these patients than in those with few or no lifetime sex partners. Given that HPV

vaccination is safe and immunogenic, and because of its potential benefit in preventing HPV-associated disease and cancer in this population, HPV vaccination is recommended for males and females with HIV aged 13 through 26 years (**AIII**). Current data do not support routine vaccination for those older than 26 years among PWH. Nonetheless, although most PWH ages 27 to 45 years would not benefit from the vaccination, some situations suggest the possibility of vaccine benefit (e.g., PWH with minimal HPV exposure). In these situations, shared clinical decision-making between the provider and patient is recommended. The public health benefit for HPV vaccination in this age range is minimal.

WVH who have been vaccinated also should have routine cervical cancer screening because the vaccine does not prevent all HPV types that may be precursors to cervical cancer, and because the vaccine may be less effective in WVH (especially those with low CD4 cell counts) than in women without HIV.

### ***Condom Use***

The use of male latex condoms is strongly recommended for preventing transmission or acquisition of HPV infection, as well as for preventing HIV and other sexually transmitted infections (STIs) (**AII**). Latex condoms provide a sufficient barrier to prevent passage of particles the size of HPV. Consistent and proper use of latex male condoms has been associated with 70% lower incidence of oncogenic HPV infection among women.<sup>18</sup> Similarly, recent cross-sectional data suggested that among heterosexual men, consistent condom use was associated with 50% lower odds of HPV infection of the penis. A meta-analysis found that condom use was associated with reduced risk of genital warts and, in women, with lower rates of CIN.<sup>128</sup> A RCT of condom use in heterosexual couples found significantly more frequent clearance of CIN and HPV among women randomized to condom use and of penile lesions among their male partners. In WVH, several studies have observed lower rates of HPV detection associated with use of condoms.

Male condoms have benefits in reducing risk of transmission of nearly all STIs (including HIV infection) during heterosexual intercourse and same-sex intercourse between men. In circumstances when a male condom cannot be used properly, a female condom (e.g., an FC1 or FC2 Female Condom<sup>®</sup>) should be considered for heterosexual vaginal intercourse (**AII**) and for heterosexual or male same-sex anal intercourse (**BIII**). Data on FC1 and FC2 Female Condoms suggest that the devices are protective against STIs.

### ***Male Circumcision***

Evidence is growing that male circumcision reduces rates of oncogenic HPV infection of the penis, based on data from RCTs<sup>129-132</sup> and observational studies. Observational studies in the general population also suggest that circumcision is associated with lower risk of penile cancer and of cervical cancer in sexual partners. Relevant data in men who are HIV seropositive, however, are limited, and the findings to date suggest that, while protective, the effects of circumcision against HPV infection may be less in PWH than in those who are HIV seronegative. Furthermore, no clinical trials have assessed whether circumcision of men who are HIV seropositive reduces risk of genital or anal HPV-related cancer or precancer (such as AIN) or oncogenic HPV infection of the anal or oral mucosa for them or their sexual partners. Evidence is insufficient to recommend adult male circumcision solely to reduce the risk of oncogenic HPV infection in men with HIV, or their sex partners, in the United States.



## Preventing Disease

### ***Preventing Vaginal and Vulvar Cancer***

Following hysterectomy for benign disease, routine screening for vaginal cancer is not recommended for women who are HIV seropositive (**AIII**). However, women with a history of high-grade CIN, adenocarcinoma in situ, or invasive cervical cancer are at increased risk and should be followed with an annual vaginal cuff Pap test (**BIII**). For patients not known to have had a hysterectomy for a benign indication, continue screening because for women with intact cervixes, studies have shown that CIN is the most common indication for hysterectomy in WWH. Although vaginal Pap tests are often abnormal in WWH and more common than in women without HIV, VAIN 2+ and vaginal cancers are infrequent.<sup>133</sup> Another study by Smeltzer *et al* in WWH with previous hysterectomy and no previous abnormal Pap test, showed that among those with vaginal biopsies, 29% had VAIN 2 or VAIN 3. However, this study was limited because the sample size was small, and it was a retrospective study. For patients with abnormal vaginal cuff Pap test results with no visible vaginal colposcopic abnormalities, the use of Lugol's iodine to stain the vagina is recommended (**AIII**). Vaginal colposcopy also is indicated in the presence of concomitant cervical and vulvar lesions. Classification of VAIN parallels that of the cervix, that is, VAIN 1, VAIN 2, and VAIN 3.

No screening procedure is available for vulvar cancer. However, biopsy or referral is indicated when inspection/palpation identifies lesions suspicious for VIN or cancer.

### ***Preventing Anal Cancer***

Some cost-effectiveness evaluations indicate that in patients who are HIV seropositive, screening for lesions using anal cytology and treating anal precancerous lesions to reduce risk of anal cancer in PWH may provide clinical benefits comparable to measures to prevent other opportunistic infection. AIN lesions are similar in many ways to CIN, but differences may exist in natural history, optimal screening, and treatment approaches to prevent cancer. At this time, no national recommendations exist for routine screening for anal cancer. However, some specialists recommend anal cytologic screening or high-resolution anoscopy (HRA) for men and women who are HIV seropositive (**CIII**). An annual digital anal examination may be useful to detect masses on palpation that could be anal cancer (**BIII**). Screening for such symptoms as anorectal bleeding, anorectal pain, and palpable anorectal masses or nodules also may be useful (**CIII**). Screening for anal cancer with anal cytology should not be done without the availability of referral for HRA. 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 Treating Disease for details on treating AIN).

### ***Preventing Oropharyngeal Cancer***

Although HPV DNA detection and HPV serology might be useful in identifying individuals at high risk of oropharyngeal cancer, no adequate methods currently exist to determine the site of HPV-associated oropharyngeal pre-cancer or cancer to target biopsy or treatment, despite ongoing efforts. It also should be noted that rates of non-HPV associated oral cancer also are increased in PWH,<sup>76</sup> and oral potentially malignant disorders can be diagnosed in some cases; albeit, the effectiveness of this approach has not been tested in RCTs.<sup>134</sup>

## Treating Disease

### *Preferred and Alternative Approaches for Treatment, Including Duration of Therapy*

#### Treating Genital and Oral Warts

PWH may have larger or more numerous warts, may not respond as well to therapy for genital warts as individuals who are immunocompetent, and may have more frequent recurrences after treatment. Genital warts are not life-threatening, and they may regress without therapy, even in PWH, especially when immunity is relatively preserved. Treatments are available for genital warts, but none are effective or preferred uniformly. Lacking RCTs specific to PWH, guidelines for the treatment of STIs in PWH should be followed. More than one treatment option may be required for refractory or recurrent lesions in PWH. Histologic diagnosis should be obtained for refractory lesions to confirm the absence of high-grade disease. Intra-anal, vaginal, or cervical warts should be treated and managed by a specialist.

Patient-applied treatments are recommended generally for uncomplicated external warts that can be identified easily and treated by the patient. Imiquimod (5% cream) is a topical cytokine inducer that should be applied at bedtime on 3 nonconsecutive nights per week, for up to 16 weeks, until lesions are no longer visible. The treatment area should be washed with soap and water 6 to 10 hours after the application (**BII**). Podofilox 0.5% solution or gel should be applied to visible anogenital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, up to four times (**BIII**). Another option is sinecatechins (15% ointment), a topical botanical product that contains active catechins from green tea and should be applied three times daily for up to 16 weeks, until warts are cleared completely and not visible (**BIII**).

No clinical trials of this latter treatment option have been conducted in PWH.

Provider-applied treatments—such as cryotherapy, trichloroacetic acid (TCA), bichloroacetic acid (BCA), and surgery—typically are recommended for complex or multicentric lesions, lesions inaccessible to patient-applied therapy, or because of patient or provider preference.

Cryotherapy (liquid nitrogen or cryoprobe) destroys lesions by thermal-induced cytolysis and should be applied until each lesion is thoroughly frozen, with treatment repeated every 1 to 2 weeks for up to 4 weeks, until lesions are no longer visible (**BIII**). Some specialists recommend allowing the lesion to thaw and freezing a second time in each session (**BIII**).

TCA and BCA (80% to 90%) each act as caustic agents to destroy wart tissue and should be applied to warts only and allowed to dry until a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. The treatment can be repeated weekly for up to 6 weeks, until lesions are no longer visible (**BIII**).

Surgical treatments (e.g., tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts (**BIII**). Laser surgery is an option, but is usually more expensive (**CIII**).

Topical application of cidofovir has reported activity against genital warts (**CIII**), but no topical

formulation is commercially available. Intralesional interferon has been used for the treatment of genital warts but because of cost, difficulty of administration, and potential for systemic adverse effects—such as fever, fatigue, myalgias, and leukopenia—it is not recommended for first-line treatment (**CIII**). Podophyllin resin may be an alternative provider-applied treatment, with strict adherence to recommendations on application. It has inconsistent potency in topical preparations, and can have toxicity that may limit routine use in clinical practice.

No consensus on optimal treatments of oral warts exists. Many treatments for anogenital warts cannot be used in the oral mucosa. Given the lack of RCTs, surgery is the most common treatment for oral warts that interfere with function or need to be removed for aesthetic reasons.

### **Treating CIN and Cervical Cancer**

WWH and CIN should be managed by a clinician with experience in colposcopy and treatment of cervical cancer precursors. In general, CIN in WWH should be managed according to American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.

Women with satisfactory colposcopy and biopsy-confirmed high-grade CIN can be treated with either ablation (e.g., cryotherapy, laser vaporization, electrocautery, diathermy, cold coagulation) or excisional methods (e.g., loop electrosurgical excision procedure, laser conization, cold knife conization), whereas women with unsatisfactory colposcopy should be treated only with excisional methods (**AII**). In patients with recurrent high-grade CIN, diagnostic excisional methods are recommended (**AII**). Hysterectomy is acceptable for treatment of recurrent or persistent biopsy-confirmed high-grade CIN (**BII**); if invasive disease is suspected, the patient should be managed in consultation with a gynecologic oncologist. The ASCCP guidelines for adolescents and young women ages 21 to 24 years should continue to be followed. In these patients, progression of lesions is more common, and so is recurrence. Therefore, close observation, as outlined in the guidelines, should be considered for management of CIN 1; CIN 2; CIN 2,3 not otherwise specified; and histologic HSIL in adolescents and WWH younger than 25 years (**BIII**). If compliance is questionable, it may be preferable to follow the treatment arm of management for CIN 2; CIN 2,3; and HSIL (**BIII**).

Management of invasive cervical cancer should follow [National Comprehensive Cancer Network \(NCCN\) guidelines](#). Although complication and failure rates may be higher in WWH, standard treatment appears safe and efficacious.<sup>93</sup>

### **Treating VIN, Vulvar Cancer, VAIN, and Vaginal Cancer**

Low-grade VIN/VAIN (VIN/VAIN1) can be observed or managed the same as vulvovaginal warts. Treatment of high-grade VIN/VAIN should be individualized in consultation with a specialist and is dependent upon the patient's medical condition and the location and extent of the disease. Various treatment modalities are available for VIN, including local excision, laser vaporization, ablation, and topical therapies (e.g., imiquimod or cidofovir<sup>135</sup> therapy). Treatment options for VAIN include topical 5-fluorouracil (5-FU), laser vaporization with CO<sub>2</sub> laser, and excisional procedures.<sup>136,137</sup>

Management of vulvar and vaginal cancer must be individualized in consultation with a specialist, following [NCCN guidelines](#).

## Treating AIN and Anal Cancer

An NIH-funded RCT to determine if treatment of anal HSIL is effective in reducing the incidence of anal cancer, the [ANCHOR Study](#), is underway. Definitive guidelines on anal screening and treatment in PWH will likely follow from the results of this study. Until then, management options for AIN 2 and 3 include treatment (with topical or ablative therapies) or active monitoring (regularly scheduled re-assessments with HRA); management decisions are based on assessment of the size and location of the lesion(s), histologic grade, and patient preference. Topical treatment options include 5-FU, imiquimod, cidofovir, and provider-applied TCA; ablative therapies include infrared coagulation, cryotherapy, laser therapy, and electrocautery/hyfreacator.<sup>138-140</sup> All treatment modalities have moderate efficacy, are well tolerated, and are associated with high rates of recurrence.<sup>141,142</sup> Repeated or combinations of treatment methods are often required for long-term clearance of AIN 2 and 3.<sup>143</sup> No indications exist for systemic chemotherapy or radiation therapy for patients with AIN in the absence of evidence of invasive cancer.

Management of anal cancer must be individualized in consultation with a specialist, following [NCCN guidelines](#).

## Treating HPV-Associated Disease at Other Sites, Including the Penis and the Oropharynx

Penile and some oropharyngeal cancers are associated with HPV infection. Treatment options do not differ for men and women with and without HIV. Data suggest a more favorable prognosis for HPV-associated oropharyngeal cancers than for non-HPV-associated oropharyngeal cancers. Surgery, chemotherapy, and radiation are treatment modalities used for oropharyngeal cancers.

## Special Considerations With Regard to Starting Antiretroviral Therapy

Given the strong evidence that early antiretroviral therapy (ART) initiation is clinically beneficial in reducing risk of AIDS and opportunistic infections (OIs), there is no reason to consider HPV-related oral, anal, or genital disease when deciding whether or when to initiate ART.

## *Monitoring Response to Therapy and Adverse Events (Including IRIS)*

Monitoring by physical examination is required during and after treatment of genital warts to detect toxicity, persistence, or recurrence, all of which are common with each of the treatments.

Because recurrences of CIN and cervical cancer after conventional therapy are more common in patients who are HIV seropositive, these individuals should be followed after treatment with frequent cytologic screening and colposcopic examination, according to published guidelines (**AI**) (see Preventing Disease and Treating Disease sections). Treatment of CIN with ablative and excisional modalities can be associated with several adverse events, such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis. Individualized treatment of adverse events is required.

Each of the treatment modalities for AIN described above is associated with adverse events, primarily pain, bleeding, ulceration, and in rare cases, development of abscesses, fissures, or fistulas. Patients can be monitored for adverse events using the methods previously described.

Treatment for anal cancer with combination radiation and chemotherapy is associated with a high rate of morbidity, even when the treatment is successful. The most important complication is

radiation-associated proctitis.

### ***Managing Treatment Failure***

For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered (**AIII**). Biopsy should be considered to exclude VIN. Genital warts often require more than one course of treatment.

Recurrent cytologic and histologic abnormalities after therapy for CIN should be managed according to ASCCP guidelines.

No consensus on the treatment of biopsy-proven recurrent VIN exists and surgical excision can be considered.

### **Preventing Recurrence**

Monitoring after therapy for cervical disease should follow ASCCP guidelines. In one study of WWH treated for high-grade CIN, low-dose intravaginal 5-FU (2 g twice weekly for 6 months) reduced the short-term risk of recurrence. Clinical experience with this therapy, however, is too limited to provide a recommendation for its use, and no follow-up study to confirm these observations has been reported. No guidelines exist regarding frequency of monitoring after therapy for VIN, but twice-yearly vulvar inspection appears reasonable for women who have been treated for VIN. Women who have been treated for high-grade VAIN should be managed like those with CIN 2, that is, with cytology at 6 and 12 months after therapy, and annually thereafter.

No indication exists for secondary prophylaxis (chronic maintenance therapy) with any of the conventional modalities to prevent recurrence of genital warts, CIN, or AIN.

### **Special Considerations During Pregnancy**

Pregnant women with HIV who have genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists, such as an obstetrician or gynecologist and an infectious disease physician. Pregnancy may be associated with an increased frequency and rate of growth of genital warts. Podofilox should not be used during pregnancy (**BIII**). At present, the evidence is insufficient to recommend imiquimod use during pregnancy (**CIII**). No anomalies have been observed with the use of imiquimod in animals during pregnancy. Several case series describe the use of imiquimod during pregnancy, also without any significant adverse effects.

Other topical treatments—such as BCA and TCA—and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy (**AIII**). Transmission of genital HPV6 and 11 from vaginal secretions at delivery is the presumed mechanism of juvenile-onset recurrent respiratory papillomatosis in children. This condition is rare but is seen more frequently among children of women who have genital warts at delivery. Cesarean delivery is not known to prevent this condition in infants and children.<sup>144</sup> No change in obstetrical management is indicated for women with genital warts unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding (**AIII**).

Pregnant women should undergo cervical cancer screening as recommended above for nonpregnant women. Cytobrush sampling can be done during pregnancy. Pregnant women with abnormal cervical cytology results should undergo colposcopy and cervical biopsy of lesions suspicious for high-grade

disease or cancer (**BIII**). Increased bleeding may occur with cervical biopsy during pregnancy. Endocervical curettage is contraindicated in pregnant women (**AIII**).

Pregnant women with ASC-US or LSIL can be managed the same as nonpregnant women, although deferral of colposcopy until at least 6 weeks postpartum is acceptable (**CIII**). Treatment of CIN is not recommended during pregnancy unless invasive disease is suspected. Pregnant women with suspected cervical cancer should be referred to a gynecologic oncologist for definitive diagnosis, treatment, and development of a delivery plan. Vaginal delivery is not recommended for women with invasive cervical cancer. For women with CIN and without suspicion of invasive disease, re-evaluation with co-testing and colposcopy is recommended after 6 weeks postpartum. Women with CIN can deliver vaginally.

At present, vaccination with commercially available HPV vaccine **is not recommended** during pregnancy (**CIII**). However, in a combined analysis of five RCTs of the HPV6/11/16/18 vaccine, administration of the vaccine to women who became pregnant during the course of the trial did not appear to negatively affect pregnancy outcomes.<sup>145</sup> Additionally, in a population-based study in Denmark, no increased risk of spontaneous abortion, stillbirth, or infant mortality was observed in more than 5,200 pregnancies exposed to at least one dose of the quadrivalent HPV vaccine. Also in Denmark, an analysis of the Medical Birth Register and National Patient Register found that among 1,665 exposed pregnancies, quadrivalent HPV vaccination was not associated with a significantly increased risk of adverse pregnancy outcomes, including major birth defect, preterm birth, or low birth weight.<sup>146</sup> Data on the use of the 9-valent vaccine during pregnancy are more limited, but to date are also reassuring.<sup>147</sup>

The effects of treatment of AIN on pregnancy are unknown. Most experts recommend deferral of diagnosis and treatment of AIN until after delivery unless a strong clinical suspicion of anal cancer exists.

## Recommendations for Cervical Cancer Screening for Women with HIV

### Women with HIV Aged <30 Years

- WWH aged 21 to 29 years should have a Pap test following initial diagnosis of HIV.
- Pap test should be done at baseline and every 12 months **(BII)**.
- If the results of three consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years **(BII)**.
- Co-testing (Pap test and HPV test) is not recommended for women younger than 30 years.

### Women with HIV Aged ≥30 Years

#### Pap Testing Only

- Pap test should be done at baseline and every 12 months **(BII)**.
- If the results of three consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years **(BII)**.

*Or*

#### Pap Test and HPV Co-Testing

- Pap test and HPV co-testing should be done at baseline **(BII)**.
- If the result of the Pap test is normal and HPV co-testing is negative, follow-up Pap test and HPV co-testing can be performed every 3 years **(BII)**.
- If the result of the Pap test is normal but HPV co-testing is positive:

*Either*

- Follow up with Pap test and perform HPV co-test in 1 year.
- If the 1-year follow-up Pap test is abnormal, or HPV co-testing is positive, referral to colposcopy is recommended.

*Or*

- Perform HPV genotyping.
  - If positive for HPV16 or HPV18, colposcopy is recommended.
  - If negative for HPV16 and HPV18, repeat co-test in 1 year is recommended. If the follow-up HPV test is positive or Pap test is abnormal, colposcopy is recommended.

*Or*

#### Pap Test and HPV16 or HPV16/18 Specified in Co-Testing

- Pap test and HPV16 or 16/18 co-testing should be done at baseline **(BII)**.
- If the result of the Pap test is normal, and HPV16 or 16/18 co-testing is negative, follow-up Pap test and HPV co-testing can be performed every 3 years **(BII)**.
- If the initial test or follow-up test is positive for HPV16 or 16/18, referral to colposcopy is recommended **(BII)**.

Primary HPV testing is not recommended **(CIII)**.

## Recommendations for Preventing Human Papillomavirus Infections

### Preventing First Episode of HPV Infection

#### *Indications for HPV Vaccination*

The target age for vaccination is 11 to 12 years **(AIII)**. Vaccination through age 26 years is recommended, but vaccine effectiveness is lower if vaccination occurs after onset of sexual activity **(BII)**.

- HPV recombinant 9-valent vaccine is not recommended for PWH ages 27 to 45 years of age or older **(AI)**. In some situations, there might be vaccine benefit (e.g., PWH with minimal HPV exposure). In these situations, shared clinical decision-making between the provider and patient is recommended. The public health benefit for HPV vaccination in this age range is minimal.

### Vaccination Schedules

HPV recombinant vaccine 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1 to 2, and 6 months **(BIII)**

- For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, some experts would give an additional full series (three doses) of vaccination with recombinant 9-valent vaccine, but no data exist to define who might benefit or how cost effective this approach might be **(CIII)**.

### Treating Condyloma Acuminata (Genital Warts)

**Note:** PWH may have larger or more numerous warts, may not respond as well to therapy for genital warts, and have a higher risk of recurrence after treatment than individuals who are HIV negative. More than one treatment option may be required for refractory or recurrent lesions. Intra-anal, vaginal, cervical, and refractory warts should be biopsied, treated, and managed by a specialist.

#### Patient-Applied Therapy

##### *For Uncomplicated External Warts That Can Be Easily Identified and Treated by the Patient*

- Imiquimod 5% cream: Apply to lesions at bedtime on three nonconsecutive nights a week, and wash the treatment area with soap and water 6 to 10 hours after application **(BII)**, repeating the cycle until lesions are no longer seen, for up to 16 weeks, *or*
- Podofilox 0.5% solution or gel: Apply to visible anogenital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, up to four times **(BIII)**, *or*
- Sinecatechins 15% ointment: Apply to area three times daily for up to 16 weeks, until warts are not visible **(BIII)**.

#### Provider-Applied Therapy

##### *For Complex or Multicentric Lesions, Lesions Inaccessible to Patient-Applied Treatments, or Patient/Provider Preference*

- Cryotherapy (liquid nitrogen or cryoprobe): Apply until each lesion is thoroughly frozen; repeat every 1 to 2 weeks for up to 4 weeks until lesions are no longer visible **(BIII)**. Some specialists allow the lesion to thaw, and then freeze a second time in each session **(BIII)**.
- TCA or BCA cauterization: 80% to 90% aqueous solution, apply to warts only and allow the area to dry until a white frost develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove



unreacted acid. Repeat treatment weekly for up to 6 weeks until lesions are no longer visible **(BIII)**.

- Surgical excision **(BIII)** or laser surgery **(CIII)** can be performed for external or anal warts.

**Key:** BCA = bichloroacetic acid; HPV = human papillomavirus; IM = intramuscular; PWH = people with HIV; TCA = trichloroacetic acid; WWH = women with HIV

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