

## HUMAN PAPILLOMAVIRUS (HPV)

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### I. INTRODUCTION

#### RECOMMENDATION:

**Diagnosis, treatment, and follow-up of HPV-related lesions in HIV-infected patients should be performed in consultation with a clinician experienced in the management of HPV and HIV.**

Human papillomaviruses (HPV) are a large group of viruses that are prevalent in the sexually active population and are capable of infecting squamous epithelia. A subgroup of approximately 30 different HPV types have a predilection for the anogenital tract and may cause asymptomatic infection, condylomata acuminata (genital warts), squamous intraepithelial neoplasia, and rarely cervical neoplasia or other anogenital carcinomas. In the United States, HPV types 16 and 18 are responsible for the development of approximately 70% of cervical and anal dysplasia and cancer. HPV types 6 and 11 account for approximately 90% of benign genital warts.<sup>1</sup> Patients infected with HPV may be infected with more than one HPV type and can be at risk for both dysplasia and benign disease.

The prevalence of HPV in HIV-infected patients is higher than in non-HIV-infected individuals and varies over time and with the degree of immunosuppression. With increased immunosuppression, anogenital warts may become extensive, may frequently relapse after treatment, and are more likely to be dysplastic.

#### **Impact of HIV Infection on the Manifestations of HPV Infection<sup>2-7</sup>**

- Condylomata acuminata, anal intraepithelial neoplasia (AIN), cervical intraepithelial neoplasia (CIN), and anal dysplasia have all been reported to occur more frequently in HIV-infected patients.
- With increased immunosuppression, there is evidence for increased risk of the following:
  - HPV infection of the genital tract
  - Development of condylomata acuminata
  - Increased severity of HPV disease
  - Anal and cervical intraepithelial neoplasia
- HPV is more difficult to treat and more likely to recur with increased immunosuppression
- Patients with AIDS have an increased relative risk of developing *in situ* or invasive genital cancers

## II. PREVENTION OF HPV

### A. HPV Vaccine

#### RECOMMENDATIONS:

**Clinicians should offer the HPV vaccine to HIV-infected women between the ages of 9 and 26 years.**

**Clinicians should continue to obtain cervical Pap tests on the recommended schedule in HIV-infected women who have been vaccinated with HPV vaccine** (see Section III: *Screening for HPV*). **Vaginal and vulvar visual inspection should be continued at regularly scheduled pelvic examinations.**

**HPV typing prior to administering the vaccine is not recommended.**

**There currently are no recommendations to vaccinate males against HPV.**

In June 2006, the Food and Drug Administration (FDA) approved the release of a quadrivalent HPV vaccine (Gardasil) that protects against disease caused by HPV types 6, 11, 16, and 18. These HPV types are associated with 70% of cervical cancers (HPV 16 and 18) and 90% of genital warts (HPV 6 and 11) in non-HIV-infected women.<sup>8</sup> The pivotal clinical trials showed that the vaccine prevented precancerous vulvar, vaginal, and cervical lesions caused by these HPV types for up to 36 months. Most studies have shown a high prevalence of HPV infections in HIV-infected individuals.<sup>9</sup>

The vaccine is FDA-approved for administration to females between the ages of 9 and 26 years.<sup>10</sup> It is administered as a three-dose regimen over a 6-month period (0, 2, and 6 months). The full regimen must be completed to confer protection. HPV vaccine has been demonstrated to provide high levels of neutralizing antibody for 5 years; the full length of its protection has not been established.

The HPV vaccine is preventive, but not therapeutic. Current studies demonstrate that the preventive efficacy of the HPV vaccine is greatest in women who are not yet sexually active and thus have not been exposed to HPV. However, HPV testing is not required before administration of the vaccine, and most women, regardless of sexual activity status, may benefit from vaccination. In the pivotal clinical trials, only 1 in a 1,000 women showed evidence of having been exposed to all four types of HPV prevented by the vaccine. Gardasil may also provide some cross-protection against HPV genotypes other than 6, 11, 16, and 18. However, additional data are required before the vaccine can be recommended for the prevention of cross-reactive HPV types.

Most of the data regarding HPV vaccine safety and efficacy are derived from studies in non-HIV-infected females. HIV-infected women may have reduced antibody response to the immunization because women who are immune suppressed have an impaired ability to mount an immune response. Studies are currently underway to provide more extensive data regarding the safety and efficacy of the vaccine in the HIV-infected population. There currently are no recommendations to vaccinate males against HPV.

Clinicians should continue to perform regular cervical screening with Pap tests and visual inspection of the vulva and vagina during annual pelvic examinations in women who have received the HPV vaccine because the vaccine does not protect against the 25% to 30% of lesions and genital cancers caused by other HPV types. Females who have not engaged in vaginal or anal penetrative sex but who have participated in sexual activity with direct genital contact should be evaluated for vulvar lesions because the virus can be passed through direct contact.

## **B. Other Strategies to Prevent HPV Infection**

### **RECOMMENDATION:**

**Clinicians should counsel HIV-infected patients on practices that may reduce the risk of acquiring HPV infection, including safe sexual practices and reduction in number of sexual partners.**

The surest way to prevent HPV infection is to abstain from any genital contact, including non-penetrative contact.<sup>11</sup> However, abstinence from sex is not an achievable goal for all patients. For those who choose to be sexually active, condom use and reduction in the number of sexual partners may reduce the risk of acquiring HPV infection. A limited number of prospective studies have demonstrated a protective effect of condoms on the acquisition of HPV<sup>12,13</sup>; however, the protection that is conferred from condom use is incomplete because HPV infection can occur in areas that are not covered by a condom, such as the scrotum, vulva, or perianus. Choosing partners who have had fewer or no previous sex partners may reduce the risk of acquiring HPV<sup>11</sup>; however, it is not possible to determine whether a partner is currently infected with HPV because most HPV-infected people are asymptomatic and may not have visible lesions.<sup>14</sup>

## **III. SCREENING FOR HPV**

### **A. Visual Inspection**

#### **RECOMMENDATION:**

**Clinicians should examine the anogenital area, including the vulva and vagina in women, to assess for visible HPV lesions at baseline and as part of the annual comprehensive physical examination.**

Clinicians should examine the anogenital area to assess for visible HPV lesions. Speculum examination of the vagina, vulva, and cervix, and anoscopic examination of the anus and lower rectum may reveal lesions as well.

### **B. Cervical Cytology**

#### **RECOMMENDATIONS:**

**Clinicians should obtain cervical Pap tests at baseline, 6 months after baseline, and then annually as long as results are normal.**

**Colposcopy should be performed for women with abnormal Pap tests. Follow-up would then vary on a case-to-case basis.**

**Clinicians should repeat Pap tests every 3 to 6 months thereafter until there have been two successive normal cervical Pap tests. Women with cervical HSIL also should be referred for high-resolution anoscopy and/or examination with biopsy of abnormal tissue**

**Clinicians should obtain at least an annual Pap test in HIV-infected women who have undergone either a supracervical or total hysterectomy.**

Screening for HPV-related dysplasia is an essential element of HIV primary care. Cervical cytologic screening with a Pap test should be performed at baseline, 6 months after baseline, and annually thereafter for HIV-infected women, if the results are normal. Follow-up colposcopy is recommended for HIV-infected women with any abnormal cervical cytologic results (see Appendix A for comparison of cytological and histological classification of cervical dysplasia). Treatment would then vary according to individual colposcopy results. After treatment, Pap tests should be repeated every 3 to 6 months until there have been two successive normal Pap tests.

Recurrent dysplasia on the vaginal cuff can be seen in women with a history of cervical dysplasia, and HIV and HPV infections both increase the risk of vaginal intraepithelial neoplasia. Therefore, women who have undergone a hysterectomy should still receive annual Pap tests.

### **C. Anal Cytology**

#### **RECOMMENDATION:**

**Clinicians should perform anal Pap tests at baseline and annually in the following populations:**

- **Men who have sex with men**
- **Any patient with a history of anogenital condylomas**
- **Women with abnormal cervical/vulvar histology**

As with cervical cancer screening, cytologic screening of the anal canal is expected to reduce the incidence of invasive anal cancer and allow the detection of precancerous dysplastic lesions or treatable early invasive disease. Analogous to cervical tissue, the anal epithelium at the dentate line has a transformation zone between squamous and columnar epithelia; this transition zone is subject to infection with and neoplastic transformation by HPV. Precancerous lesions of the anal squamous epithelium can develop and are classified as low- or high-grade according to identical Bethesda criteria and nomenclature developed for grading cervical lesions (see Appendix A). High-grade lesions may progress to invasive disease.<sup>15</sup> Pap tests of the anal canal are simple to perform, clinically effective, and cost-effective to reduce the incidence of invasive disease in high-risk individuals.<sup>16,17</sup> Anal Pap testing using a Dacron swab is a well-validated technique with comparable sensitivity and specificity to cervical cytology.<sup>18</sup> For more guidance regarding anal Pap tests, refer to [Neoplastic Complications](#), Section V: [Anal Dysplasia and Cancer](#).

## D. HPV DNA Testing

### RECOMMENDATION:

**HPV DNA testing in HIV-infected patients is *not* recommended at this time.**

HPV DNA testing has been FDA-approved for 1) use in non-HIV-infected women with ASC-US cervical Pap test results to determine which patients should receive follow-up colposcopy and which women should receive a follow-up Pap test in 1 year, 2) use in non-HIV-infected women  $\geq 30$  years of age as a routine adjunctive screening with cervical Pap test. It is currently recommended that colposcopy be performed in all HIV-infected women with any abnormal cervical cytology and anoscopy be performed in all HIV-infected patients with abnormal anal cytology. Therefore, the results of HPV testing do not change the management of HIV-infected patients with abnormal cervical or anal cytology.<sup>18</sup>

Studies that determined that HPV types can be divided into oncogenic and non-oncogenic types were performed in non-HIV-infected populations. There are no studies of the natural history of HPV types in the HIV-infected population. It is not known whether non-oncogenic HPV types behave in an oncogenic fashion in the setting of HIV and/or immune suppression. In addition, patients may be infected with more than one type of HPV; however, current tests detect only the most prevalent types. Patients with prominent non-oncogenic HPV types and minor species of oncogenic types may be incorrectly triaged to low-risk follow-up.

## IV. PRESENTATION AND DIAGNOSIS

### RECOMMENDATIONS:

**Clinicians should include HPV in the differential diagnosis of anogenital symptoms, such as itching, bleeding, pain, or spotting after sexual intercourse.**

**Patients with abnormal anogenital physical findings, such as warts, hypopigmented or hyperpigmented plaques/lesions, lesions that bleed, or any other lesions of uncertain etiology, should be referred for high-resolution anoscopy, a cervical Pap test (for women), and/or examination with biopsy of abnormal findings.**

Diagnosis of external condylomata acuminata is usually made on the basis of clinical appearance. The appearance of warts is protean. Condylomata acuminata (genital warts) are smooth skin-colored or pigmented papules or plaques that may be flat, hyperkeratotic, nodular or exophytic. Symptoms may include itching, bleeding, burning, and discomfort. Warts on the female genitalia and cervix are most commonly flat, white, plaque-like lesions, best visualized by colposcopy, but also can be exophytic and visible to the eye. Oral warts are white, flat-topped, or exophytic papules with stippled or papillated surfaces.

Small external lesions often are treated without biopsy. Lesions that are atypical or variegated in color or shape require biopsy to exclude intraepithelial dysplasia. Clinicians should maintain a low threshold to obtain biopsy of atypical-appearing lesions; pigmented, internal, condylomatous lesions; and lesions that fail to respond to repeated courses of treatment.

Liquid phase hybridization, filter hybridization (Southern blot and slot blot hybridization), *in situ* hybridization, and polymerase chain reaction (PCR) are used to determine HPV type. The use of HPV DNA testing in HIV-infected patients is not recommended at this time. For patients who are presumed to be non-HIV-infected, HPV testing can be a useful adjunct when Pap test results are ASC-US. It is currently recommended that colposcopy be performed in all HIV-infected women with any abnormal cervical cytology and anoscopy be performed in all HIV-infected patients with abnormal anal cytology. Therefore, the results of HPV testing do not change the management of HIV-infected patients with abnormal cervical or anal cytology.

## V. TREATMENT

### RECOMMENDATIONS:

**Clinicians should use the same therapeutic modalities to treat HPV in HIV-infected patients as those used in non-HIV-infected patients (see Table 1). The following factors should be considered when choosing treatment:**

- **Patient preference**
- **Clinician experience and available resources**
- **Size of wart(s) and number of warts**
- **Anatomic site of wart(s)**
- **Adverse effects of treatment**

**Clinicians should switch treatment modalities if warts have not improved substantially within 3 months of therapy. For condyloma that have not responded to treatment, clinicians should obtain biopsy to exclude dysplasia or cancer.**

**Clinicians should not use podophyllotoxin or interferon in pregnant women.**

**Clinicians should refer patients with lesions that are resistant to simple therapies, lesions that change in appearance, and lesions with ulceration, irregular shape, or variegated coloration to clinicians experienced in the management of HPV and HIV.**

**Primary care clinicians should refer HIV-infected patients with cervical, vulvar, or anal cancer to an oncologist for treatment** (see [Neoplastic Complications](#) and *Anogenital Neoplasia* guidelines for further discussion regarding treatment of cancer).

Treatment of condyloma is aimed at removing symptomatic visible warts. However, untreated warts may resolve spontaneously. To date, there has been no evidence that any available treatment regimen eradicates infection. Comparative efficacy trials of the different treatment options for HIV-infected patients have not been conducted.

Cryotherapy, podophyllotoxin, interferon, imiquimod, cidofovir gel, trichloroacetic acid (TCA), and bichloroacetic acid (BCA) have all been studied in small numbers of HIV-infected patients with mixed results. All studies showed shrinkage in wart size for most patients but less than complete resolution for a significant proportion of patients.

Clinicians often report poor clearance rates after therapy in HIV-infected patients with advanced immunosuppression. More than one application of therapy, more than one method of treatment (e.g., topical imiquimod followed by cryotherapy), or longer duration of treatment is often needed. The treatment modality should be changed if a patient has not improved substantially within 3 months of therapy. The response to treatment and its side effects should be evaluated throughout the course of therapy.

Although there are cases of involution of mucocutaneous warts after initiation of HAART, the prevalence or course of HPV anogenital disease is not usually significantly altered by ARV treatment. There are no data available regarding effects of HPV treatment on transmissibility.

| <b>TABLE 1</b>  |  |
|---|--|
| <b>AVAILABLE TREATMENT OPTIONS FOR CONDYLOMA</b>  |  |
| <b>Patient-Applied Treatments</b>   | <b>Provider-Applied Treatments</b>   |
| <ul style="list-style-type: none"> <li>▪ Podophyllotoxin<sup>a</sup></li> <li>▪ Imiquimod<sup>b</sup></li> <li>▪ Cidofovir gel</li> </ul> | <ul style="list-style-type: none"> <li>▪ Cryotherapy</li> <li>▪ Podophyllin resin<sup>a</sup></li> <li>▪ Trichloroacetic acid</li> <li>▪ Bichloroacetic acid 80%-90%</li> <li>▪ Interferon alfa-2b<sup>a</sup></li> <li>▪ Electrodesiccation</li> <li>▪ Surgical excision</li> <li>▪ Laser (carbon dioxide, pulsed-dye)</li> <li>▪ Loop electrosurgical excision procedure (LEEP)</li> <li>▪ Infrared coagulation</li> </ul> |

<sup>a</sup> Should not be used in pregnant women. TCA or BCA can be used to treat small external warts during pregnancy but may not be as effective.

<sup>b</sup> May decrease likelihood of recurrences.

## **VI. MANAGEMENT OF PARTNERS**

### **RECOMMENDATION:**

**Clinicians should consider both the HIV exposure and the STI exposure to partners when HIV-infected patients present with a new STI. Clinicians should also assess for the presence of other STIs.**

### **A. Management of HIV Exposure in Partners**

#### **RECOMMENDATIONS:**

**When HIV-infected patients present with a new STI, clinicians should offer assistance with notifying partners of both the potential HIV and STI exposures or should refer patients to other sources for partner notification assistance ([Partner Services](#) in New York State or [CNAP](#) in New York City). Partners without confirmed HIV infection should undergo HIV testing at baseline, 1, 3, and 6 months. Confirmatory testing according to New York State regulations must be performed to confirm HIV diagnoses.**

Clinicians should educate patients with non-HIV-infected partners or partners of unknown HIV status to be vigilant for any post-exposure acute HIV symptoms in their partners, such as febrile illness accompanied by rash, lymphadenopathy, myalgias, and/or sore throat (see [Diagnosis and Management of Acute HIV Infection](#)). (AIII)

Partners who present within 36 hours of an HIV exposure should be evaluated as soon as possible for initiation of post-exposure prophylaxis therapy (see [HIV Prophylaxis Following Non-Occupational Exposure Including Sexual Assault](#)). (AII)

Presentation of a new STI in HIV-infected patients suggests exposure of both HIV and the STI to their partners. In this case, offering HIV non-occupational post-exposure prophylaxis (nPEP) to partners is usually not an option because the period prior to STI symptom onset is usually longer than the 36-hour window for initiating HIV nPEP. Therefore, sequential HIV testing of partners without confirmed HIV infection should be performed for early identification of potential HIV acquisition. However, if a patient with an HIV exposure does present within 36 hours, evaluation for nPEP should occur (see [HIV Prophylaxis Following Non-Occupational Exposure Including Sexual Assault](#)).

## **B. Management of HPV Exposure**

### **RECOMMENDATIONS:**

**For sex partners of patients with genital warts, clinicians should:**

- **Examine sex partners for the presence of genital warts and other STIs**
- **Counsel female sex partners about the importance of cervical cytologic screening**

Treatment of genital warts solely for the purpose of preventing future transmission cannot be recommended because the value of treatment in reducing infectivity is unknown. However, sex partners of patients who have genital warts might benefit from counseling and examination to assess the presence of genital warts and other STIs.<sup>19</sup>

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## APPENDIX A

### COMPARISON OF CYTOLOGICAL AND HISTOLOGICAL CLASSIFICATION OF CERVICAL AND ANAL DYSPLASIA

| Comparison of Cytological and Histological Classification of Cervical Dysplasia |   |  |
|---|---|--|
| Bethesda Classification (2001)<br>(cytology)                                    | Cervical Intraepithelial Neoplasia (CIN)<br>(histology) | WHO Terminology<br>(cytology)                                      |
| ASC-US<br>ASC-H   | Atypia  |  |
| LSIL  | CIN I   | Mild dysplasia   |
| HSIL  | CIN II<br>CIN III<br>CIS                                | Moderate dysplasia<br>Severe dysplasia<br>Carcinoma <i>in situ</i> |
| Cancer  | Cancer  | Cancer   |

ASC-H: atypical squamous cells, HSIL cannot be excluded; ASC-US: atypical squamous cells of undetermined significance; CIS: carcinoma *in situ*; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

| Comparison of Cytological and Histological Classification of Anal Dysplasia |   |  |
|---|---|--|
| Bethesda Classification<br>(cytology)                                       | Anal Intraepithelial Neoplasia (AIN)<br>(histology) | WHO Terminology<br>(cytology)                                      |
| ASC-US<br>ASC-H   | Atypia  |  |
| LSIL  | AIN I   | Mild dysplasia   |
| HSIL  | AIN II<br>AIN III<br>CIS                            | Moderate dysplasia<br>Severe dysplasia<br>Carcinoma <i>in situ</i> |
| Cancer  | Cancer  | Cancer   |

ASC-H, atypical squamous cells, HSIL cannot be excluded; ASC-US, atypical squamous cells of undetermined significance; CIS, carcinoma *in situ*; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.