# Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents



Downloaded from https://aidsinfo.nih.gov/guidelines on 2/17/2019

# Human Papillomavirus Disease (Last updated November 29, 2018; last reviewed November 29, 2018)

## Epidemiology

Human papillomavirus (HPV) infection is the major risk factor for development of cervical cancer,[1,2] the fourth most common cancer in women worldwide.[3,4] Nearly all cervical cancers test positive for HPV genetic sequences,[5-7] most notably the E6 and E7 oncogenes,[8-10] which are thought to play a major role in immortalization of cervical epithelial cells.[11]

Cervical infection with HPV is common and occurs primarily through sexual transmission.[12-16] Penetrative sexual intercourse is not strictly necessary for HPV transmission,[17] but it is the primary risk factor for HPV infection, and HPV prevalence is low in young women who report only non-penetrative sexual contact.[17,18] The vast majority of cervical HPV infections resolve or become latent and undetectable, but in a subset of women, infection persists.[12,19,20] Persistence of oncogenic HPV infection is a necessary step in HPV-related cervical tumorigenesis,[1,21,22] although it appears insufficient for final cell transformation.[11] At least 12 HPV types are considered oncogenic, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[22-24] 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 are not considered oncogenic.[22-24]

In the United States and Western Europe, women with HIV/AIDS have significantly higher rates of cervical cancer than women in the general population,[25-31] and recent cohort data show a direct relationship between low CD4 T lymphocyte (CD4) cell count and cervical cancer risk.[32] In Africa, the data are more limited and inconsistent,[33] but a prospective registry-based study found increased risk of cervical cancer in women with HIV/AIDS.[34] HIV infection and low CD4 cell count also have been consistently and strongly associated with HPV infection itself and with precancerous cervical lesions, including low-grade cervical intraepithelial neoplasia (CIN), and the precursor to cervical cancer, CIN 3.[35-47] Higher rates of HPV infection and CIN are seen in adolescents with HIV, regardless of whether HIV was acquired vertically or horizontally.[36,48,49] 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 were also common in this group, with a cumulative rate of 12% by age 19 years.

Other cancers caused by HPV include most anal cancers and a subset of tumors of the vulva, vagina, penis, oral cavity, and oropharynx.[1,23,50-52] HPV16 is the type present in most HPV-positive non-cervical cancers.[1,23,50,53,54] Patients with HIV/AIDS also have a significantly elevated incidence of these tumors relative to the general population,[25,55,56] and CD4 cell count has been related to risk of anal cancer.[32] 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,[57-59] as are anal and genital warts, and in women, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).[60-62] In the U.S. general population, HPV also causes approximately 70% of oropharyngeal cancers (OPC)[63,64]; HPV16 causes 84% of HPV-associated OPC, and the HR HPV types contained in the nine-valent HPV vaccine cause approximately 94%.[65] HPV-associated OPC incidence is four- to five-fold higher in males than in females,[66] and two- to three-fold higher among individuals with HIV infection.[67]

Despite the associations between HIV and CD4 cell count and HPV-related cancers and precancers, the impact of antiretroviral therapy (ART) on the incidence of HPV-related tumors is uncertain, and it is possible that the impact differs by tumor type. Some studies found decreased persistence/progression of CIN with ART,[68] including a study that distinguished between adherent and non-adherent ART use.[69] Although several prior studies found the incidence of cervical cancer itself unchanged,[55] and reported that anal cancer incidence was increasing[55] more recent registry-based results have found significant decreases in cervical and

anal cancer risk in men and women with HIV infection.[70] Conversely, use of ART did not affect CIN rates in adolescents with perinatally or horizontally acquired HIV.[36,49] The incidence of high-grade VIN was not reduced with ART use, even though rates of low-grade vulvar lesions and anal or genital warts did decrease with ART,[60] and some[71,72] but not other[73,74] studies reported increased rates of oral warts following ART initiation.

Overall, whether the burden of HPV-related cancers will decrease or even increase over time is difficult to currently gauge, as the risk of these cancers in individuals with HIV infection remains high relative to the general population, even if these differences are moderately decreasing. Further, the successful prolongation of life with use of ART for HIV suppression can also lead to increasing cumulative incidence of tumors over time, as well as potentially longer duration of HPV persistence, and accumulation of somatic mutations and epigenetic changes that contribute to carcinogenesis. This clinical scenario may be of particular concern for HPV-related cancers, such as anal cancers, that are not currently subject to routine screening. However, increasing use of HPV vaccination in adolescents and young adults may begin to reduce the risk of HPV-associated cancers in persons with HIV infection in later life.

## 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.[75]

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 cm 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 may also 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 patients HIV infection.[76]

### *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.

### *Cervical Cancer Screening Recommendations*

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.

Possible Pap test results include:

- 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)
- ASCUS (atypical squamous cells of undetermined significance)
- ASC-H (atypical squamous cells, cannot rule out a high-grade lesion)
- AGC (atypical glandular cells)

## Women With HIV Infection Aged <30 years

### *Screening*

The Pap test is the primary mode for cervical cancer screening for women with HIV infection <30 years of age. Screening for these women should commence within 1 year of the onset of sexual activity regardless of mode of HIV transmission (e.g., sexual activity, perinatal exposure) but no later than age 21 years. Women with HIV infection 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 infection is normal, the next Pap test should be in 12 months **(BII)**. Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**. If the results of the 3 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 women with HIV infection <30 years of age.

### *Abnormal Pap Test Results*

For ASC-US Pap test, if reflex HPV testing is positive, a referral to colposcopy is recommended. If HPV testing is not available or not done, 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 (regardless of reflex HPV result, if done).

### *Rationale*

These recommendations reflect evidence that women with HIV infection <21 years of age and sexually active may have a high rate of progression of abnormal cytology[36] **(BII)**. No similar prospective data are available for adolescents who acquired HIV during the perinatal period, but as noted earlier, Brogly and colleagues reported that 30% of such adolescents had ASC-US or greater on their first cervical Pap test.[49] The mean age at the time of the first Pap test was 16.7 years, with a range of 13 to 23 years.

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

## Women With HIV Infection Aged ≥30 years

Cervical cancer screening in women with HIV infection 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, the woman with HIV infection should have a Pap test at the time of HIV diagnosis (baseline), then every 12 months **(BII)**. Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**. If the results of the 3 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 16 or 16/18 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, then referral to colposcopy is recommended. If the HPV testing is positive, but the genotype specific testing for HPV16 or HPV 16/18 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 ≥ASC-US on repeat cytology, referral to colposcopy is recommended **(AII)**.

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 **(AII)**. For any result ≥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 (regardless of HPV result, if done).

### *Rationale*

Current guidelines from both the American Cancer Society and the U.S. Preventive Services Task Force allow for use of HPV co-testing with cytology. A negative HPV test predicts prolonged low risk of cancer. Cytology/HPV co-testing can allow for a prolonged cervical cancer screening interval in women with HIV infection 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 as women with HIV infection 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*

There are three FDA-approved HPV vaccines: 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, and anal cancer and genital warts due to vaccine types based on randomized clinical trial (RCT) data.[77-79,80-83] Although there are no efficacy data with the 9-valent HPV vaccine in men, a clinical trial established the safety of the vaccine in young men aged 16 to 26 years and showed similar antibody concentrations as in the young women aged 16 to 26 years in whom efficacy was established.[84]

Although there are no clinical trials to demonstrate HPV vaccine efficacy in prevention of oropharyngeal cancers, there is some evidence that the prevalence of oral vaccine-type HPV infections are reduced with vaccination.[85,86] One prospective trial of the quadrivalent HPV vaccine in adults with HIV infection older than 27 years suggested efficacy for prevention of oral HPV infection.[87]

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with 9 valent HPV vaccine for all 11- or 12-year-old girls and boys. The vaccine series can be started at age 9 years. Catch-up vaccination is recommended for all 13- to 26-year-old females and all 13- to 21-year-old males who have not been vaccinated. Catch-up vaccination is also recommended for males aged 22 to 26 years who are men who have sex with men (MSM), or have HIV infection or are otherwise immunocompromised.[88,89]

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.[88,89] Although ACIP recommends a 2-dose schedule for adolescents initiating the vaccine series at ages 9 to 14 years,[90] three doses of HPV vaccine (0, 1–2, and 6 months) are recommended for females and males with HIV infection 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 adults with HIV infection older than 27 years.[87] 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[91,92] in a broad range of individuals with HIV infection.[93] Some studies have demonstrated lower antibody levels in individuals with HIV infection than in those who do not have are HIV infection; however, the clinical significance of this observation is unknown.[94-96] Studies have shown that HPV vaccination induces an anamnestic response in children and adults with HIV infection.[92,97,104] Immune responses appear stronger among those with higher CD4 counts and suppressed HIV viral loads.[93,98,96]

For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, many experts would give additional full series of vaccination with recombinant 9-valent vaccine, but there are no data 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 depending on location in U.S. men and women.[65]

HPV vaccination prevents initial HPV infection and is ideally administered before sexual exposure to HPV. Because some individuals with HIV infection 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 infection aged 13 through 26 years **(AIII)**.

Current data do not support vaccination for those older than 26 years, and HPV vaccines are not approved for use in men or women older than 26 years. Women with HIV infection who have been vaccinated should also 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 women with HIV infection (especially those with low CD4 cell counts) than in women without HIV infection.

## *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 diseases (STDs) **(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.[18] 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.[99] 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 women with HIV infection, 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 STDs (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®) 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 STDs.

### *Male Circumcision*

Evidence is growing that male circumcision reduces rates of oncogenic HPV infection of the penis, based on data from RCTs[100-103] 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 individuals with HIV infection 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 infection, 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 as for women with intact cervices as studies have shown that CIN is the most common indication for hysterectomy in women with HIV infection. Although vaginal Pap tests are often abnormal in women with HIV infection and more common than in women without HIV infection, VAIN 2+ and vaginal cancers are infrequent.[104] Another study by Smeltzer et al in women with HIV infection with previous hysterectomy and no previous abnormal Pap test, showed that among those with vaginal biopsies, 29% had VAIN 2 or VAIN 3. However, there were limitations to this study as 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 patients with HIV

infection may provide clinical benefits comparable to measures to prevent other opportunistic infection. AIN lesions are similar in many ways to CIN, but there may be differences 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 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 anal cancer with anal cytology should not be done without the availability of referral for high resolution anoscopy. If anal cytology is performed and indicates ASC-US, then ASC cannot rule out ASC-H, LSIL, or high-grade squamous intraepithelial lesion (HSIL), then it should be followed by high-resolution anoscopy **(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 on treating AIN).

### *Preventing Oropharyngeal Cancer*

While HPV DNA detection and HPV serology might be useful in identifying individuals at high risk of oropharyngeal cancer, there are currently no adequate methods to determine the site of HPV-associated oropharyngeal pre-cancer or cancer to target biopsy or treatment, despite ongoing efforts. It should also be noted that rates of non-HPV associated oral cancer are also increased in individuals with HIV infection,[67] and oral potentially malignant disorders (OPMDs) can be diagnosed in some cases; albeit, the effectiveness of this approach has not been tested in RCTs.[105]

## Treating Disease

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

#### Treating Genital and Oral Warts

Patients with HIV infection 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 patients with HIV, especially when immunity is relatively preserved. Treatments are available for genital warts, but none are uniformly effective or uniformly preferred. Lacking RCTs specific to individuals with HIV infection, guidelines for the treatment of STDs in patients with HIV infection should be followed. More than one treatment option may be required for refractory or recurrent lesions in patients with HIV infection. 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 generally recommended for uncomplicated external warts that can be easily identified and treated by the patient. Imiquimod (5% cream) is a topical cytokine inducer that should be applied at bedtime on three non-consecutive 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 completely cleared and not visible **(BIII)**.

No clinical trials of this latter treatment option have been conducted in individuals with HIV infection.

Provider-applied treatments such as cryotherapy, trichloroacetic acid (TCA), bichloroacetic acid (BCA), and surgery, are typically 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 side 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.

There is no consensus on optimal treatments of oral warts. 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

Women with HIV infection and CIN should be managed by a clinician with experience in colposcopy and treatment of cervical cancer precursors. In general, CIN in women with HIV infection should be managed according to ASCCP guidelines.

Women with satisfactory colposcopy and biopsy-confirmed high-grade CIN can be treated with either ablation (i.e., cryotherapy, laser vaporization, electrocautery, diathermy, and 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. For adolescents with HIV infection, the ASCCP guidelines for adolescents and young women 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, CIN2,3 not otherwise specified, and histologic HSIL in HIV-infected adolescents and women younger than 25 years **(BIII)**. If compliance is questionable, then it may be preferable to follow the treatment arm of management for CIN 2, CIN2,3, and HSIL **(BIII)**.

Management of invasive cervical, vaginal, and vulvar cancer should follow National Comprehensive Cancer Network (NCCN) guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Although complication and failure rates may be higher in women with HIV infection, standard treatment appears safe and efficacious.

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

Low-grade VIN/VAIN (VIN/VAIN1) can be observed or managed as for 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 imiquimod therapy. Treatment options for VAIN include topical 5-fluorouracil (5-FU), laser vaporization with CO2 laser, and excisional procedures with electrosurgical loops or a scalpel excision.

Management of vulvar and vaginal cancer must be individualized in consultation with a specialist, following NCCN guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).

### Treating AIN and Anal Cancer

For AIN2-3, no adequate RCTs have been reported, and data are insufficient to recommend a specific treatment approach. A RCT was recently initiated to determine if treatment of AIN2-3 reduces the incidence of anal cancer in patients with HIV infection. Definitive guidelines on anal screening and treatment in patients with HIV infection will likely follow from the results of this study. Until then, treatment decisions are based on assessment of the size and location of the lesion and its histologic grade. **All treatment modalities are associated with high rates of recurrence.** Topical treatment options including 5-FU, cidofovir, intra-anal imiquimod, and provider-applied TCA have demonstrated moderate efficacy for treatment of intra-anal AIN. Ablative therapies including infrared coagulation, cryotherapy, laser therapy, and electrocautery/hyfrecator are well tolerated. Repeated ablative treatment or a combination of treatment methods are often required for long-term clearance of AIN2-3.

In a retrospective analysis, infrared coagulation was proven to have moderate efficacy in treatment of AIN-2 or 3 in patients who are HIV seropositive,[106] and it was safe and well tolerated in this population in a prospective AIDS Malignancy Consortium study. No indications exist for systemic chemotherapy or radiation therapy for patients with AIN in the absence of evidence of invasive cancer.

The most commonly used treatment for anal cancer is combination radiation and chemotherapy.

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

Penile and some oropharyngeal cancers are associated with HPV infection. Treatment options do not differ for men and women with and without HIV infection. 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 ART

Given the strong evidence that early 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, they should be followed after treatment with frequent cytologic screening and colposcopic examination, according to published guidelines **(AII)** (see Preventing Disease and Treating 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.

There is no consensus on the treatment of biopsy-proven recurrent VIN and surgical excision can be considered.

## Preventing Recurrence

Monitoring after therapy for cervical disease should follow ASCCP guidelines. In one study of women with HIV infection 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 living with HIV infection who have genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists (such as an obstetrician/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. There have been several case series describing 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 early-onset recurrent respiratory papillomatosis in children. This condition is rare but is more common among children of women who have genital warts at delivery. Cesarean delivery is not known to prevent this condition in infants and children.[107] 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 non-pregnant 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 can be managed the same as non-pregnant women, although deferral of colposcopy until at least 6 weeks postpartum is recommended **(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 cytology and colposcopy is recommended after 6 weeks postpartum. Women with CIN can deliver vaginally. An analysis of the Danish Medical Birth Register and National Patient Register found that among 1665 exposed pregnancies, quadrivalent HPV vaccination was not associated with a significantly increased risk of adverse pregnancy outcome.[108]

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.[109]

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 Infection

**Women with HIV Infection Aged <30 Years:**

- If younger than 21 years, known to have HIV infection or newly diagnosed HIV infection, and sexually active, screen within 1 year of onset of sexual activity regardless of mode of HIV infection.
- Women with HIV infection 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)**.
- Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**
- If results of 3 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 Infection Aged ≥30 Years**

*Pap Testing Only:*

- Pap test should be done at baseline and every 12 months **(BII)**.
- Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**.
- If results of 3 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 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 test with Pap test and HPV co-testing should be performed 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 HPV-16 or HPV-18, colposcopy is recommended
  - If negative for HPV-16 and HPV-18, 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 HPV 16 or HPV 16/18 Specified in Co-Testing:*

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

### Recommendations for Preventing Human Papillomavirus Infections

**Preventing First Episode of HPV Infection**

*Indications for HPV Vaccination:*

- HIV-infected; aged 13 to 26 years **(AIII)**

**Note:** Please refer to Pediatric OI Guidelines for vaccination of boys and girls younger than age 13 years.

**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 **(AIII)**

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

**Treating Condyloma Acuminatum (Genital Warts)**

**Note:** Patients with HIV infection 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 maybe required for refractory or recurrent lesions. Intra-anal, vaginal, or cervical warts should be 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 3 non-consecutive 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*
- Sinecatechins 15% ointment: Apply to area 3 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 to Acronyms:** BCA = bichloroacetic acid; HPV = human papillomavirus; IM = intramuscular; OI = opportunistic infection; TCA = trichloroacetic acid

## References


1. World Health Organization International Agency for Research on Cancer. Volume 90: Human Papillomaviruses. 2007. In. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France.
2. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007;370(9590):890-907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17826171.
3. American Cancer Society. Global Cancer Facts & Figures 3rd Edition. Atlanta: American Cancer Society; 2015. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-3rd-edition.pdf.
4. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-2917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21351269.
5. Bosch FX, Manos MM, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J Natl Cancer Inst*. 1995;87(11):796-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7791229.

6. Wheeler CM, Hunt WC, Joste NE, Key CR, Quint WG, Castle PE. Human papillomavirus genotype distributions: implications for vaccination and cancer screening in the United States. *J Natl Cancer Inst*. 2009;101(7):475-487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19318628.

7. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. 2003;348(6):518-527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12571259.

8. Kraus I, Molden T, Holm R, et al. Presence of E6 and E7 mRNA from human papillomavirus types 16, 18, 31, 33, and 45 in the majority of cervical carcinomas. *J Clin Microbiol*. 2006;44(4):1310-1317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16597856.

9. Castle PE, Dockter J, Giachetti C, et al. A cross-sectional study of a prototype carcinogenic human papillomavirus E6/E7 messenger RNA assay for detection of cervical precancer and cancer. *Clin Cancer Res*. 2007;13(9):2599-2605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17473189.

10. Ratnam S, Coutlee F, Fontaine D, et al. Clinical performance of the PreTect HPV-Proofer E6/E7 mRNA assay in comparison with that of the Hybrid Capture 2 test for identification of women at risk of cervical cancer. *J Clin Microbiol*. 2010;48(8):2779-2785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20573862.

11. Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. *Clin Sci (Lond)*. 2006;110(5):525-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16597322.

12. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998;338(7):423-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9459645.

13. Winer RL, Feng Q, Hughes JP, O'Reilly S, Kiviat NB, Koutsky LA. Risk of female human papillomavirus acquisition associated with first male sex partner. *J Infect Dis*. 2008;197(2):279-282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18179386.

14. Bauer HM, Hildesheim A, Schiffman MH, et al. Determinants of genital human papillomavirus infection in low-risk women in Portland, Oregon. *Sex Transm Dis*. 1993;20(5):274-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8235925.

15. Wheeler CM, Parmenter CA, Hunt WC, et al. Determinants of genital human papillomavirus infection among cytologically normal women attending the University of New Mexico student health center. *Sex Transm Dis*. 1993;20(5):286-289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8235927.

16. Burk RD, Ho GY, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. *J Infect Dis*. 1996;174(4):679-689. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8843203.

17. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol*. 2003;157(3):218-226. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12543621.

18. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med*. 2006;354(25):2645-2654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16790697.

19. Moscicki AB, Shiboski S, Broering J, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr*. 1998;132(2):277-284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9506641.

20. Evander M, Edlund K, Gustafsson A, et al. Human papillomavirus infection is transient in young women: a population-based cohort study. *J Infect Dis*. 1995;171(4):1026-1030. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7706782.

21. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst*. 2010;102(5):315-324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20157096.

22. Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. *Infect Agent Cancer*. 2009;4:8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19486508.

23. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. 2009;10(4):321-322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19350698.

24. Castle PE. The evolving definition of carcinogenic human papillomavirus. *Infect Agent Cancer*. 2009;4:7. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/19432962.

25. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst*. 2000;92(18):1500-1510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10995805.
26. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst*. 2009;101(16):1120-1130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19648510.
27. Simard EP, Engels EA. Cancer as a cause of death among people with AIDS in the United States. *Clin Infect Dis*. 2010;51(8):957-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20825305.
28. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst*. 2005;97(6):425-432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15770006.
29. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*. 2007;370(9581):59-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17617273.
30. Dal Maso L, Polesel J, Serraino D, et al. Pattern of cancer risk in persons with AIDS in Italy in the HAART era. *Br J Cancer*. 2009;100(5):840-847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19223894.
31. Polesel J, Franceschi S, Suligoi B, et al. Cancer incidence in people with AIDS in Italy. *Int J Cancer*. 2010;127(6):1437-1445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20049835.
32. Guiguet M, Boue F, Cadranel J, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol*. 2009;10(12):1152-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19818686.
33. Orem J, Otieno MW, Remick SC. AIDS-associated cancer in developing nations. *Curr Opin Oncol*. 2004;16(5):468-476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15314517.
34. Mbulaiteye SM, Katabira ET, Wabinga H, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. *Int J Cancer*. 2006;118(4):985-990. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16106415.
35. Strickler HD, Burk RD, Fazzari M, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2005;97(8):577-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15840880.
36. Moscicki AB, Ellenberg JH, Crowley-Nowick P, Darragh TM, Xu J, Fahrat S. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. *J Infect Dis*. 2004;190(8):1413-1421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15378433.
37. Schrager LK, Friedland GH, Maude D, et al. Cervical and vaginal squamous cell abnormalities in women infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1989;2(6):570-575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2555473.
38. Maiman M, Fruchter RG, Serur E, Remy JC, Feuer G, Boyce J. Human immunodeficiency virus infection and cervical neoplasia. *Gynecol Oncol*. 1990;38(3):377-382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2227552.
39. Ahdieh L, Klein RS, Burk R, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis*. 2001;184(6):682-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11517428.
40. Schuman P, Ohmit SE, Klein RS, et al. Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. *J Infect Dis*. 2003;188(1):128-136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12825181.
41. Massad LS, Riester KA, Anastos KM, et al. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. Women's Interagency HIV Study Group. *J Acquir Immune Defic Syndr*. 1999;21(1):33-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10235512.
42. Feingold AR, Vermund SH, Burk RD, et al. Cervical cytologic abnormalities and papillomavirus in women infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1990;3(9):896-903. Available at: http://www.ncbi.

nlm.nih.gov/pubmed/2166784.

43. Wright TC, Jr., Ellerbrock TV, Chiasson MA, Van Devanter N, Sun XW. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors, and validity of Papanicolaou smears. New York Cervical Disease Study. *Obstet Gynecol*. 1994;84(4):591-597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8090399.
44. Sun XW, Ellerbrock TV, Lungu O, Chiasson MA, Bush TJ, Wright TC, Jr. Human papillomavirus infection in human immunodeficiency virus-seropositive women. *Obstet Gynecol*. 1995;85(5 Pt 1):680-686. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7724095.
45. Heard I, Jeannel D, Bergeron C, Saada M, Henrion R, Kazatchkine MD. Lack of behavioural risk factors for squamous intraepithelial lesions (SIL) in HIV-infected women. *Int J STD AIDS*. 1997;8(6):388-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9179650.
46. Delmas MC, Larsen C, van Benthem B, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. *AIDS*. 2000;14(12):1775-1784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10985315.
47. Six C, Heard I, Bergeron C, et al. Comparative prevalence, incidence and short-term prognosis of cervical squamous intraepithelial lesions amongst HIV-positive and HIV-negative women. *AIDS*. 1998;12(9):1047-1056. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9662202.
48. Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. *J Infect Dis*. 2004;190(1):37-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15195241.
49. Brogly SB, Watts DH, Ylitalo N, et al. Reproductive health of adolescent girls perinatally infected with HIV. *Am J Public Health*. 2007;97(6):1047-1052. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17463385.
50. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. *Vaccine*. 2006;24 Suppl 3:S3/11-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16949997.
51. Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. *J Adolesc Health*. 2010;46(4 Suppl):S20-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20307840.
52. Grulich AE, Jin F, Conway EL, Stein AN, Hocking J. Cancers attributable to human papillomavirus infection. *Sex Health*. 2010;7(3):244-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20719211.
53. Smith JS, Backes DM, Hoots BE, Kurman RJ, Pimenta JM. Human papillomavirus type-distribution in vulvar and vaginal cancers and their associated precursors. *Obstet Gynecol*. 2009;113(4):917-924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19305339.
54. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. 2009;124(7):1626-1636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19115209.
55. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. *Arch Intern Med*. 2010;170(15):1337-1345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20696958.
56. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer*. 2008;123(1):187-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18435450.
57. Wilkin TJ, Palmer S, Brudney KF, Chiasson MA, Wright TC. Anal intraepithelial neoplasia in heterosexual and homosexual HIV-positive men with access to antiretroviral therapy. *J Infect Dis*. 2004;190(9):1685-1691. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15478076.
58. Kreuter A, Brockmeyer NH, Hochdorfer B, et al. Clinical spectrum and virologic characteristics of anal intraepithelial neoplasia in HIV infection. *J Am Acad Dermatol*. 2005;52(4):603-608. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15793509.
59. Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *AIDS*. 2005;19(13):1407-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16103772.
60. Massad LS, Silverberg MJ, Springer G, et al. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. *Am J Obstet Gynecol*. 2004;190(5):1241-

1248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15167825.

61. Conley LJ, Ellerbrock TV, Bush TJ, Chiasson MA, Sawo D, Wright TC. HIV-1 infection and risk of vulvovaginal and perianal condylomata acuminata and intraepithelial neoplasia: a prospective cohort study. *Lancet*. 2002;359(9301):108-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11809252.

62. Jamieson DJ, Paramsothy P, Cu-Uvin S, Duerr A, Group HIVERS. Vulvar, vaginal, and perianal intraepithelial neoplasia in women with or at risk for human immunodeficiency virus. *Obstet Gynecol*. 2006;107(5):1023-1028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648406.

63. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969503.

64. Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012;30 Suppl 5:F12-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23199955.

65. Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst*. 2015;107(6):djv086. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25925419.

66. Viens LJ, Henley SJ, Watson M, et al. Human Papillomavirus-Associated Cancers - United States, 2008-2012. *MMWR Morb Mortal Wkly Rep*. 2016;65(26):661-666. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27387669.

67. Beachler DC, Abraham AG, Silverberg MJ, et al. Incidence and risk factors of HPV-related and HPV-unrelated Head and Neck Squamous Cell Carcinoma in HIV-infected individuals. *Oral Oncol*. 2014;50(12):1169-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25301563.

68. Ahdieh-Grant L, Li R, Levine AM, et al. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2004;96(14):1070-1076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15265968.

69. Minkoff H, Zhong Y, Burk RD, et al. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. *J Infect Dis*. 2010;201(5):681-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20105077.

70. Hernandez-Ramirez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV*. 2017;4(11):e495-e504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28803888.

71. King MD, Reznik DA, O'Daniels CM, Larsen NM, Osterholt D, Blumberg HM. Human papillomavirus-associated oral warts among human immunodeficiency virus-seropositive patients in the era of highly active antiretroviral therapy: an emerging infection. *Clin Infect Dis*. 2002;34(5):641-648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11803508.

72. Greenspan D, Canchola AJ, MacPhail LA, Cheikh B, Greenspan JS. Effect of highly active antiretroviral therapy on frequency of oral warts. *Lancet*. 2001;357(9266):1411-1412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11356441.

73. Greenspan D, Gange SJ, Phelan JA, et al. Incidence of oral lesions in HIV-1-infected women: reduction with HAART. *J Dent Res*. 2004;83(2):145-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14742653.

74. Hamza OJ, Matee MI, Simon EN, et al. Oral manifestations of HIV infection in children and adults receiving highly active anti-retroviral therapy [HAART] in Dar es Salaam, Tanzania. *BMC Oral Health*. 2006;6:12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16916469.

75. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356(19):1944-1956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494927.

76. Workowski KA, Berman S, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1-110. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21160459.

77. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet*. 2009;374(9686):301-314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19586656.

78. Group FIS. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*.

2007;356(19):1915-1927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494925.

79. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372(8):711-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25693011.
80. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. 2011;365(17):1576-1585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22029979.
81. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med*. 2011;364(5):401-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21288094.
82. Joura EA, Leodolter S, Hernandez-Avila M, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet*. 2007;369(9574):1693-1702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17512854.
83. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007;356(19):1928-1943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494926.
84. Castellsague X, Giuliano AR, Goldstone S, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26144901.
85. Herrero R, Quint W, Hildesheim A, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. *PLoS One*. 2013;8(7):e68329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23873171.
86. Sonawane K, Suk R, Chiao EY, et al. Oral human papillomavirus infection: differences in prevalence between sexes and concordance with genital human papillomavirus infection, NHANES 2011 to 2014. *Ann Intern Med*. 2017;167(10):714-724. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29049523.
87. Wilkin TJ, Chen H, Cespedes MS, et al. A randomized, placebo-controlled trial of the quadrivalent HPV vaccine in HIV-infected adults age 27 years or older: AIDS Clinical Trials Group protocol A5298. *Clin Infect Dis*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29659751.
88. Centers for Disease C, Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males--Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(50):1705-1708. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22189893.
89. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63(RR-05):1-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25167164.
90. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination - updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2016;65(49):1405-1408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27977643.
91. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr*. 2010;55(2):197-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20574412.
92. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. *J Infect Dis*. 2010;202(8):1246-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20812850.
93. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis*. 2014;59(1):127-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24723284.
94. Rainone V, Giacomet V, Penagini F, et al. Human papilloma virus vaccination induces strong human papilloma virus specific cell-mediated immune responses in HIV-infected adolescents and young adults. *AIDS*. 2015;29(6):739-743. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25849837.
95. Faust H, Toft L, Sehr P, et al. Human papillomavirus neutralizing and cross-reactive antibodies induced in HIV-positive subjects after vaccination with quadrivalent and bivalent HPV vaccines. *Vaccine*. 2016;34(13):1559-1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26896686.

96. Money DM, Moses E, Blitz S, et al. HIV viral suppression results in higher antibody responses in HIV-positive women vaccinated with the quadrivalent human papillomavirus vaccine. *Vaccine*. 2016;34(40):4799-4806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27544584.

97. Ellsworth GB, Lensing SY, Ogilvie CB, et al. A delayed dose of quadrivalent human papillomavirus vaccine demonstrates immune memory in HIV-1-infected men. *Papillomavirus Res*. 2018;6:11-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29807211.

98. Kahn JA, Xu J, Kapogiannis BG, et al. Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women. *Clin Infect Dis*. 2013;57(5):735-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23667266.

99. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis*. 2002;29(11):725-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12438912.

100. Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in Orange Farm, South Africa. *J Infect Dis*. 2009;199(1):14-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19086814.

101. Tobian AA, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Engl J Med*. 2009;360(13):1298-1309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19321868.

102. Serwadda D, Wawer MJ, Makumbi F, et al. Circumcision of HIV-infected men: effects on high-risk human papillomavirus infections in a randomized trial in Rakai, Uganda. *J Infect Dis*. 2010;201(10):1463-1469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20370481.

103. Gray RH, Serwadda D, Kong X, et al. Male circumcision decreases acquisition and increases clearance of high-risk human papillomavirus in HIV-negative men: a randomized trial in Rakai, Uganda. *J Infect Dis*. 2010;201(10):1455-1462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20370483.

104. Massad LS, Xie X, Greenblatt RM, et al. Effect of human immunodeficiency virus infection on the prevalence and incidence of vaginal intraepithelial neoplasia. *Obstet Gynecol*. 2012;119(3):582-589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22353957.

105. Balasundaram I, Payne KF, Al-Hadad I, Alibhai M, Thomas S, Bhandari R. Is there any benefit in surgery for potentially malignant disorders of the oral cavity? *J Oral Pathol Med*. 2014;43(4):239-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23750566.

106. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. *Dis Colon Rectum*. 2005;48(5):1042-1054. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15868241.

107. Fife KH, Katz BP, Brizendine EJ, Brown DR. Cervical human papillomavirus deoxyribonucleic acid persists throughout pregnancy and decreases in the postpartum period. Am J *Obstet Gynecol*. 1999;180(5):1110-1114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10329863.

108. Scheller NM, Pasternak B, Molgaard-Nielsen D, Svanstrom H, Hviid A. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. *N Engl J Med*. 2017;376(13):1223-1233. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28355499.

109. Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. *Obstet Gynecol*. 2009;114(6):1179-1188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19935017.