Screening for Anal Dysplasia and Cancer in Patients with HIV

Medical Care Criteria Committee, with Gina Brown, MD1, March 2020

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1Dr. Brown’s most recent participation in the MCCC was from 2013 until 2019, during which time she served as a contributing member and as lead author of the guidelines on HPV and cervical screening. She was lead author of this guideline until her departure. Dr. Brown also served on the Perinatal Guidelines Committee and on the Women’s Health Committee.
Screening for Anal Dysplasia and Cancer in Patients with HIV

Purpose and Development of this Guideline

**Purpose:** This guideline on screening for anal cancer and dysplasia in individuals with HIV was developed by the Medical Care Criteria Committee (MCCC) of the New York State (NYS) Department of Health (DOH) AIDS Institute (AI) Clinical Guidelines Program. Its purpose is to inform clinicians in NYS who provide primary care to individuals with HIV about human papillomavirus (HPV)-related anal disease and to identify opportunities for screening and treatment. Accordingly, this guideline addresses the following topics: HPV transmission, prevention, and screening, and the diagnosis, follow-up, and treatment of HPV-related anal disease.

The goal of this guideline is to provide standards for clinicians in NYS to identify HPV-related anal disease in individuals with HIV and provide currently available treatment and follow-up and to:

- Increase the numbers of NYS residents with HIV who are screened and effectively treated for HPV-related anal and perianal dysplasia.
- Support the NYSDOH Prevention Agenda 2019-2024 to decrease the burden of HPV by educating care providers on the importance of HPV vaccination and by increasing the rate of 3-dose HPV immunization among individuals with HIV.
- Reduce the morbidity and mortality associated with HPV-related anal and perianal disease in individuals with HIV through early identification and treatment of potentially precancerous and cancerous lesions, when treatment is most likely to be effective.

**Development:** This guideline was developed by the NYSDOH AI Clinical Guidelines Program, which is a collaborative effort between the NYSDOH AI Office of the Medical Director and the Johns Hopkins University School of Medicine, Division of Infectious Diseases.

Established in 1986, the goal of the Clinical Guidelines Program is to develop and disseminate evidence-based, state-of-the-art clinical practice guidelines to improve the quality of care throughout NYS for people who have HIV, hepatitis C virus, or sexually transmitted infections; people with substance use issues; and members of the LGBTQ community. NYSDOH AI guidelines are developed by committees of clinical experts through a consensus-driven process.

The NYSDOH AI charged the Medical Care Criteria Committee with developing evidence-based clinical recommendations for screening for anal cancer and dysplasia in individuals with HIV. The resulting recommendations are based on an extensive review of the medical literature and reflect consensus among this panel of experts. Each recommendation is rated for strength and quality of the evidence (see below). If recommendations are based on expert opinion, the rationale for the opinion is included.

### AIDS Institute Clinical Guidelines Program: Recommendations Ratings (updated June 2019)

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<tr>
<th>Strength of Recommendation Ratings</th>
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<tr>
<td>A</td>
<td>Strong recommendation</td>
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<th>Quality of Supporting Evidence Ratings</th>
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<tr>
<td>1</td>
<td>Indicates that the evidence supporting a recommendation is derived from published results of at least one randomized trial with clinical outcomes or validated laboratory endpoints.</td>
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* Indicates that the evidence supporting a recommendation is strong because it is: 1) based on a self-evident conclusion(s); 2) conclusive, published, in vitro data; or 3) well-established, accepted practice that cannot be tested because ethics would preclude a clinical trial.
With limited and conflicting data on screening and management of anal dysplasia, many of the recommendations included here are based on the expert opinions of experienced clinicians. Research underway now, such as the Anal Cancer HSIL Outcomes Research study (the ANCHOR study), is expected to provide additional evidence in support of early identification and treatment of HPV-related anal disease.

**Burden and Implications of HPV-Related Anal Disease in Individuals With HIV**

The American Cancer Society estimates 8,300 new cases of anal cancer for 2019 in the general population: 2,770 in men and 5,530 in women [ACS 2019]. These numbers represent a decrease in cases (2,950) among men in 2017 and an increase in cases among women (5,250) [ACS 2017]. According to the Centers for Disease Control and Prevention, anal cancer rates for 2011 to 2015 were 2.2 per 100,000 person-years among women and 1.3 per 100,000 person-years among men [CDC 2018]. Men living with HIV, and particularly men who have sex with men (MSM), have higher rates of anal human papilloma virus (HPV) disease than other populations. The incidence of anal cancer in MSM with HIV was 131 per 100,000 person-years between 1996 and 2007 [Palefsky 2017]. HPV-associated cancers occur more often among individuals with HIV than in the general population [Jemal, et al. 2013; Thompson, et al. 2018].


**HPV Type and Anal Dysplasia**

The relationship between specific HPV types and HPV-related anal disease is still under study, but it has been estimated that HPV infection is responsible for approximately 91% of anal cancers, including anal and rectal SCC [CDC 2018]. A wide range and high prevalence of HPV types responsible for oncogenic and non-oncogenic HPV-related anal disease have been documented in individuals with HIV [Clifford, et al. 2006; Kojic, et al. 2011; Liu, et al. 2018]. HPV type 16 is the most common high risk type among individuals with or without HIV [Lin, et al. 2018]. However, among MSM with HIV, many other HPV types are found [Alcorn 2018]. Infection with more than 1 HPV type occurs more frequently among individuals with HIV, which can put them at risk for cervical, vulvar, perianal or anal squamous intraepithelial lesions (SIL), and cancer [Clifford, et al. 2006; Castilho, et al. 2015].
KEY POINT

- Infection with more than 1 HPV type occurs more frequently among individuals with HIV, and such individuals can be at risk for cervical, vulvar, and perianal or anal SIL.

HIV and Anal Cancer Risk


Other risk factors associated with anal dysplasia include hepatitis B virus in MSM with HIV [Aldersley, et al. 2018], lower CD4 count [Tandon, et al. 2010; Baranoski, et al. 2012], and cigarette smoking [Bertisch, et al. 2013; Poljak, et al. 2017]. Some data suggest that immune reconstitution with the use of antiretroviral therapy (ART) reduces but does not eliminate the risk of anal cancer [van der Snoek, et al. 2012; Palefsky 2017]. The effects of ART and other interventions used to alter the course of HPV-related anal disease in individuals with HIV and prevent anal cancer are currently being studied [ANCHOR 2018].

HPV and Anal Dysplasia in Men

A 2012 meta-analysis found the incidence of anal cancer to be 45.9 per 100,000 among MSM with HIV and 5.1 per 100,000 among MSM who did not have HIV [Machalek, et al. 2012]. In MSM with HIV, receptive anal intercourse is the most common risk factor for anal cancer, likely reflecting concurrent HPV infection.

HIV is also associated with a higher risk of anal cancer among men who have sex with women (MSW), although the risk is lower than it is for MSM. In a multicenter cohort study, the incidence of anal cancer among men with HIV was substantially higher than among men who did not have HIV [Silverberg, et al. 2012]. In a single-center, retrospective cohort study of 221 individuals with HIV, 28% of MSW had abnormal anal cytology, compared with 48% of MSM [Gandra, et al. 2015]. In that report, the majority of the abnormalities were atypical squamous cells of undetermined significance. Among those with abnormal anal cytology or high-risk HPV who underwent high resolution anoscopy (HRA), 39% of MSM, 25% of women, and 12% of MSW had high-grade anal intraepithelial neoplasia, representing 16%, 5%, and 2%, respectively, of the total numbers screened. However, since populations based on sexual practices were not prospectively screened, these data cannot be used to estimate prevalence of HPV disease to guide a general screening recommendation.

HPV and Anal Dysplasia in Women

Women with HIV have a higher incidence of anal cancer than women without HIV. A multicenter study that included 8,842 women with HIV and 11,653 women without HIV reported an anal cancer incidence of 30 per 100,000 person-years among women with HIV and no cases among those without [Silverberg, et al. 2012]. Women with HIV are significantly more likely to have abnormal anal cytology or histology results than women without HIV, with the rates in some studies similar to those reported among men with HIV [Frisch, et al. 2000; Dal Maso, et al. 2009; Hessol, et al. 2009; Tandon, et al. 2010; Baranoski, et al. 2012; Gandra, et al. 2015; Stier, et al. 2015]. A multicenter trial reported a 27% prevalence of anal HSIL among women with HIV [Stier, et al. 2019].

Although abnormal cervical cytology results are a risk factor for abnormal anal cytology results, women may have anal dysplasia without concomitant cervical disease. In some studies, the prevalence of HPV-related anal disease was higher than HPV-related cervical disease in women [Kojic, et al. 2011; Gaisa M, et al. 2017], supporting the recommendation to screen all women with HIV for HPV-related anal disease regardless of cervical cytology (Pap test) results.

Anal Dysplasia Progression to Anal Carcinoma

Progression from anal dysplasia to anal cancer is slower than the progression from cervical dysplasia to cervical cancer [Machalek, et al. 2012; Roberts JR, et al. 2017; Stewart, et al. 2018]. However, similar to the natural history of cervical cancer, it is generally accepted that anal dysplasia is the precursor to invasive anal carcinoma.

There are limited data to support the notion of a stepwise progression from low-grade SIL (LSIL) to HSIL to invasive carcinoma, but 2 studies documented a progression to HSIL at the same site as the initial LSIL [Berry, et al. 2014; Liu, et al. 2018]. In a prospective study, 41% of individuals with HIV who had LSIL at baseline developed HSIL during the 20-month follow-up period. The majority (84%) of HSIL were situated at the site of the baseline LSIL [Liu, et al. 2018]. In a retrospective study, anal cancers were documented at the site of previously biopsied HSIL; the average time for progression from diagnosis of HSIL to anal cancer was 5 years [Berry, et al. 2014].

Spontaneous regression of anal dysplasia, including HSIL, has also been described. In a randomized clinical trial, HSIL resolved among nearly one-third of participants in the active monitoring group that did not receive treatment [Goldstone SE, et al. 2019]. In a retrospective study, HSIL spontaneously regressed in 20% of participants with HIV [Tong, et al. 2013]. At this time, there are no data to guide assessment of lesions to determine which ones will progress, persist, or regress.

→ KEY POINT

- Smoking is strongly associated with anal cancer and with increased risk for anal cancer recurrence. Smoking cessation should be promoted for all patients with HIV, especially those at increased risk for anal cancer [Ramamoorthy, et al. 2008; Bowzyk Al-Naeeb, et al. 2014].

Transmission and Prevention of HPV

RECOMMENDATIONS: Transmission and Prevention of HPV

- Clinicians should recommend the 9-valent human papillomavirus (HPV) vaccine 3-dose series at 0, 2, and 6 months to all individuals who are 9 to 26 [a] years of age with HIV regardless of CD4 cell count, prior cervical or anal cytology (Pap test) results, HPV test results, HPV-related cytologic changes, or other history of HPV-related lesions. (A3)
- Clinicians should engage patients who are 27 to 45 years of age in shared decision-making regarding HPV vaccination. (A3)

a. In October 2018, the U.S. Food and Drug Administration (FDA) changed its HPV vaccination recommendations to include ages 27 to 45. There was no specific mention of HIV [U.S. FDA 2018].

HPV Vaccine

The FDA has approved a bivalent HPV vaccine that protects against oncogenic HPV types 16 and 18 (Cervarix); a quadrivalent vaccine that protects against non-oncogenic HPV types 6 and 11 and oncogenic HPV types 16 and 18 (Gardasil); and a 9-valent vaccine that protects against non-oncogenic HPV types 6 and 11 and oncogenic HPV types 16, 18, 31, 33, 45, 52, and 58 (Gardasil 9).

Because it offers broader coverage of HPV types, the 9-valent vaccine is the only HPV vaccine available in the United States (see the Centers for Disease Control and Prevention [CDC] Supplemental information and guidance for vaccination providers regarding use of 9-valent HPV for more information). The HPV vaccine is FDA-approved for preventive but not therapeutic use. There are currently no data to support the use of the HPV vaccine to ameliorate existing anal dysplasia.

Extrapolating data from the demonstrated effectiveness of the quadrivalent HPV vaccine in older individuals [Wilkin, et al. 2016], the FDA expanded the age range for recommended HPV vaccination in the United States from ages 9 to 26 years to include individuals who are 27 to 45 years of age [U.S. FDA 2018]. There is no specific mention of HIV infection in the updated FDA recommendation. Although 1 study demonstrated lower efficacy of the quadrivalent vaccine in individuals with HIV [Wilkin, et al. 2016], other research linked HIV viral suppression to vaccine efficacy [Money, et al. 2016].
When to Vaccinate

HPV vaccination may be scheduled at the same time as standard adolescent vaccines offered at age 11 or 12 years. For young people who have experienced sexual abuse or assault or who are immunocompromised, the vaccine series should begin at age 9 [Glidden, et al. 2016]. In the general population, a 2-dose HPV vaccine is recommended for individuals younger than 15 years, and a 3-dose vaccine regimen is recommended for individuals aged 15 and older [CDC 2016]. For individuals with HIV who are 9 to 45 years of age, the 3-dose HPV vaccine remains the recommended approach [Meites, et al. 2016]. The 9-valent HPV vaccine should be administered according to the CDC standard schedule for immunocompromised adults, children, and adolescents (a 3-dose regimen over a 6-month period at 0, 2, and 6 months) [Kojic, et al. 2014] and should be offered regardless of CD4 cell count.

HPV vaccination provides high levels of neutralizing antibody for at least 5 years and is protective in individuals aged 26 years or younger who do not have HIV, regardless of history of sexual activity; however, the full length of its protection has not been established. Although data are limited, the immunogenicity of the quadrivalent HPV vaccine has been demonstrated in individuals with HIV [Wilkin, et al. 2018].

**HPV testing and vaccination:** HPV testing is not recommended before vaccine administration. It is unlikely that an individual will have been infected with all the HPV types covered by the 9-valent vaccine; therefore, it is expected that the 9-valent HPV vaccine will be effective against any of the 9 HPV types or any HPV types to which the individual has not been exposed. There also may be beneficial prevention due to cross-reactivity with other HPV types not included in the 9-valent vaccine [Wheeler, et al. 2012].

Revaccination with the 9-valent HPV vaccine is not currently recommended for individuals who previously received the bivalent or quadrivalent HPV vaccine [Petrosky, et al. 2015]. Vaccination with the quadrivalent HPV vaccine has demonstrated cross-protection against other oncogenic HPV types [Kemp, et al. 2011]. Clinicians may consider the benefit of protection against the additional 5 oncogenic HPV types targeted in the 9-valent vaccine for individual patients [CDC 2016]. If a scheduled vaccine dose is missed, there is no need to repeat doses; there is no maximum interval [CDC 2019].

Other Forms of HPV Prevention

HPV infection is the most common sexually transmitted infection (STI) in the United States, and many individuals become infected with multiple types of HPV during their lives [CDC 2013]. HPV is transmitted via skin-to-skin contact, so barrier methods, such as male and female condoms, offer some, but not full protection. Because prior identification of HPV infection in a sexual partner is unlikely, limiting the number of sexual partners may reduce but not eliminate an individual's exposure to HPV [Winer, et al. 2003].

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**KEY POINTS**

- In individuals with HIV, the 9-valent HPV vaccine is administered in 3 doses at months 0, 2, and 6.
- HPV testing is not recommended before administration of the HPV vaccine.
Screening

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<th>RECOMMENDATIONS: Screening</th>
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<tr>
<td>• For all patients with HIV ≥35 years old, regardless of HPV vaccine status, clinicians should:</td>
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<tr>
<td>- Inquire annually about anal symptoms, such as itching, bleeding, palpable masses or nodules, pain, tenesmus, or a feeling of rectal fullness. (A2)</td>
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<tr>
<td>- Perform a visual inspection of the perianal region. (A3)</td>
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<tr>
<td>- Provide information about anal cancer screening and engage the patient in shared decision-making regarding screening, including anal cytology prior to digital anorectal examination (DARE). (A3)</td>
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<tr>
<td>- Perform DARE if anal symptoms are present. (A*)</td>
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<tr>
<td>• Clinicians should promote smoking cessation for all patients with HIV, especially those at increased risk for anal cancer.</td>
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<tr>
<td>• For all patients with HIV ≥35 years old, clinicians should recommend and perform annual DARE to screen for anal pathology (B3)</td>
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<tr>
<td>• Clinicians should evaluate any patient with HIV who is &lt;35 years old and presents with signs or symptoms that suggest anal dysplasia. (A3)</td>
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<tr>
<td>• Clinicians should conduct or refer for high resolution anoscopy (HRA) and histology (via biopsy) any patient with abnormal anal cytology. (A2)</td>
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<tr>
<td>• Clinicians should refer patients with suspected anal cancer determined by DARE or histology to an experienced specialist for evaluation and management. (A3)</td>
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b. The perianal area is a 5 cm radius from the anal verge. In women the vulvar and perianal areas overlap.

Rationale for Screening

Screening for HPV-related anal disease is a relatively new recommendation, and data on the benefit of screening and immediate treatment interventions are not yet definitive. Anal cancer screening and assessment is modeled after cervical cancer screening, which is based on early identification of squamous intraepithelial lesions (SIL), follow-up to monitor for disease progression, and interventions to prevent disease progression and cancer (see the NYSDOH AI guideline Cervical Screening for Dysplasia and Cancer). Based on the available epidemiologic evidence and the benefits of the analogous cervical screening, this Committee has recommended anal screening for specific subpopulations of individuals with HIV since 2007. The current recommendation is expanded to include anal cytology screening for MSM, cisgender women, transgender women, and transgender men who have HIV and are ≥35 years. Anal cytology for screening is not currently recommended for men who have sex with women (MSW); however, clinicians may perform anal cytology testing for any patient with HIV who requests it. If clinicians have previously adopted screening for anal cancer, including anal cytology, HRA, and treatment in younger individuals, they may engage their patients in shared decision-making regarding ongoing screening or deferral until age 35. Considerations that may be weighed in the discussion include cytology results, HPV HR status, previously identified ASC-H/HSIL, and previous treatment.

Anal dysplasia and invasive carcinoma are often asymptomatic. Screening and close follow-up of individuals with HIV and with high-grade squamous intraepithelial lesions (HSIL) can detect pre-neoplastic lesions and cancers at an early stage, before clinical presentation of symptoms, and reduce mortality [Cajas-Monson, et al. 2018; Stewart, et al. 2018; Revollo, et al. 2019]. Five-year survival rates for early stage anal cancer are much higher than for late-stage disseminated disease (80% vs. 32%) [NCI SEER 2015]. A prospective study found that more than half of MSM with HIV reported at least 1 anal symptom, but there was no association between anal symptoms and presence of HSIL [Goddard, et al. 2019]. In another prospective study of HIV-infected MSM with HSIL, nearly half of those who developed anal cancer were asymptomatic [Berry, et al. 2014].

The reported rate of anal cancer among individuals with HIV is currently higher than the rate of cervical cancer before adoption of universal screening programs. HIV infection is now recognized as an independent risk factor for anal HSIL and progression to anal cancer among MSM, MSW, and women (see Burden and Implications of HPV-Related Anal Disease in...
Individuals With HIV. It should be noted that anal dysplasia and cancer can develop even in the absence of anal sex or cervical disease, therefore screening is recommended independent of additional risk factors.

HPV typing: HPV typing has been used to stratify the risk of cervical cancer and follow-up in women with low-grade cervical disease and post-treatment for high-grade disease. Its direct applicability to HPV-related anal disease screening and treatment in men and women is still under study. High-risk HPV infection was associated with anal HSIL in several studies [Machalek, et al. 2016; Lin, et al. 2018; Clarke Megan A, et al. 2019]; however, the high prevalence of HPV among MSM with HIV limits the usefulness of the test in that population.

A meta-analysis from the National Cancer Institute found overall high sensitivity but low specificity of HPV testing for anal cancer screening, especially in studies limited to MSM with HIV [Clarke M. A. and Wentzensen 2018]. Although HPV 16/18 genotyping increases specificity, the sensitivity remains unacceptably low. A large study conducted mostly in MSM (44% with HIV) found that screening with anal cytology plus high-risk HPV testing significantly improved the sensitivity and negative predictive value beyond cytology alone [Sambursky, et al. 2018]. However, available data are not sufficient to assess the performance of HPV typing in other populations. Current data are inconclusive regarding the role of HPV typing to screen for anal cancer or guide its treatment.

Safety: Screening for anal cancer does have some negative effects, but it is generally safe. Anal cytology testing is both safe and well tolerated. HRA and biopsy are safe but may be less well tolerated because of discomfort during the procedure and pain and potential bleeding after biopsy. Patients may experience anxiety while waiting for test results or when they learn the results. Careful patient education and explanation of the benefits and nature of the procedures and the meaning of results may help alleviate anxiety and improve tolerability [Russo, et al. 2018]. Some studies have reported higher levels of discomfort or anxiety among some subpopulations, specifically younger MSM and women [Steele, et al. 2012; Leeds and Fang 2016; De-Masi, et al. 2018; Lam, et al. 2018; Ong, et al. 2018].

Clinicians should follow current recommendations for cervical screening in women as presented in the NYSDOH AI guideline Cervical Screening for Dysplasia and Cancer.

→ KEY POINT

- The utility of HPV typing for the management of anal disease is unknown.

When to Conduct Screening

Although data support screening for anal cancer in MSM with HIV at certain ages [Chiao, et al. 2008; Piketty, et al. 2008], there are no data to support specific age recommendations for screening other individuals with HIV. Until there are additional data, the age recommendations for screening are the same for all individuals with HIV.

Delayed diagnosis of anal cancer is common [Ristvedt, et al. 2005; Chiu, et al. 2015]. MSM may have benign conditions such as fissures or sexually transmitted infections (STIs) that can mask the diagnosis. The average age at which anal cancer is diagnosed in the general population is in the early 60s. Anal cancer is diagnosed at younger ages (40 to 49 years) in individuals with HIV than in those who do not have HIV [Chiao, et al. 2008; Piketty, et al. 2008]. In MSM, a diagnosis of anal cancer is rare before age 25 years [Brickman and Palefsky 2015]; therefore, this committee recommends initiation of routine screening at age 35 years in individuals with HIV [Deshmukh, et al. 2017]. The higher incidence of and younger age at anal cancer diagnosis in individuals with HIV, the lack of knowledge about HPV pathogenesis in the anus, and the morbidity associated with delayed diagnosis warrant screening at this younger age to detect abnormalities before progression to cancer.

The upper age limit for anal cancer screening has not been established. Clinicians may consider discontinuing screening in patients older than 75 years who have had 3 consecutive negative screening test results and who are no longer sexually active.

Histopathologic Classification of Anal Cytology

The Bethesda Classification System for reporting cervical cytology terminology has been used for reporting anorectal cytology results that may require further follow-up because many parallels exist between cervicovaginal and anorectal screening. SIL of the anal squamous mucosa are classified as low-grade (LSIL) or high-grade (HSIL). Although an LSIL does not typically progress to cancer, an HSIL is considered the precursor lesion to invasive carcinoma; however, anal cytology
may not correlate closely with histology. Therefore, any abnormal result should prompt the clinician to perform or refer for HRA or histology (via biopsy).

When a Pap test finds atypical squamous cells (ASCs) of undetermined significance (ASC-US), the lesion cannot be distinguished as low-grade or high-grade. ASC-US and ASC-H lesions require follow-up as described in the section *Follow-Up of Abnormal Cytology Results*.

**Anal Cytology Tests**


Anogenital examination to assess for visible HPV lesions is necessary because HPV can also infect the urethra and the external genitalia [Weyers, et al. 2010; Tyerman and Aboulafia 2012; Leeds and Fang 2016; Ehrenpreis and Smith 2018]. Direct visualization of the perianal skin, anus, and lower rectum (via standard anoscopy) may also reveal lesions.

An anal cytology sample can be obtained by inserting a moistened nylon or polyester swab into the rectum. Cytologic sampling should include the transformation zone [Roberts JM, et al. 2016]. If anal cytology test results are not adequate for interpretation, for any reason, the test should be repeated. Patients should be advised not to perform an enema or douche prior to cytologic screening.

**Performing an Anal Cytology Test**

- Perform an anal cytology test before using swabs for other STI testing, using lubricant, or performing a DARE.
- A moistened nylon or polyester swab may be used to obtain an anal cytology sample according to the laboratory authority’s collection instructions (cotton swabs should not be used). See *University of California San Francisco Anal Cancer Information > Obtaining a specimen for anal cytology* for detailed instructions.
- Instruct patients to refrain from performing an anal enema or douche, engaging in anal sex, or inserting any objects into the anus for 24 hours prior to cytologic screening.

Anal cytology testing is a well-validated technique. When compared with anal histology, the sensitivity and specificity of anal cytology are similar to those of cervical cytology [Fox, et al. 2005]. Among patients with HIV, the sensitivity of anal cytology was 90% when CD4 count was ≤400 cells/mm³ and 67% when CD4 count was >400 cells/mm³ \( (P=.005) \) [Mathews, et al. 2010]. In patients with HIV, the positive and negative predictive values of cytologic samples collected using a swab were virtually identical to cytologic samples collected with direct visualization using HRA [Mathews, et al. 2010]. Studies of self-collected samples for anal cytology are small and demonstrate variable reliability when compared with clinician-collected samples [Cranston, et al. 2004; McNeil, et al. 2016]. Although self-collected anal swabs can be used to determine the presence of HPV types, additional studies are needed to determine the utility of HPV identification and typing for anal disease management when used with cytologic screening.

If a rectal swab for anal screening is performed and testing for gonococcal and chlamydial infection is also performed, then swabs can be obtained sequentially, with anal cytologic samples obtained first.

**Direct Visualization and Biopsy via High Resolution Anoscopy (HRA)**

Abnormal anal cytology results should be followed by direct visualization via HRA and directed biopsy. As with cervical disease, histologic diagnosis is required to make a diagnosis and guide interventions for anal disease. (See *University of California San Francisco (UCSF) Anal Cancer Information > DARE and HRA* for a detailed description of the procedure.)

As with cervical carcinoma, HSILs (the precursors to invasive carcinoma) are generally asymptomatic. Colonoscopy does not screen for anal cancer and is not an acceptable alternative to HRA. Individuals with anal cancer may complain of thickening and irritation of the perianal skin, itching, bleeding, tenesmus, pain with defecation, constipation, change in stool caliber, or pain during receptive anal sex. Anorectal bleeding, which is the most common presenting symptom of anal cancer, is often mistakenly attributed to hemorrhoids. Only 30% of individuals with anal cancer experience pain or
the sensation of an anal mass [Abbas, et al. 2010]. Visual inspection can identify abnormal anal physical findings, such as warts, hypopigmented or hyperpigmented plaques/lesions, or lesions that bleed.

Among individuals with anal warts or other lesions, anal cytology alone may not be adequate to detect HSIL [Papaconstantinou, et al. 2005]. Tissue that has an HSIL may be buried within or under the visible lesion, therefore it is reasonable to advise HRA for such patients even if cytology is benign. Patients with perianal warts may have concurrent intra-anal warts and HSILs. Visual inspection of warts may not correctly predict histologic abnormality. Larger, persistent, or variegated-appearing lesions may require biopsy by trained clinicians to determine histology and exclude HSIL in individuals with HIV.

Digital Anorectal Examination (DARE)

DARE is recommended as a companion to anal cytology for anal cancer screening. The International Anal Neoplasia Society has developed practice guidelines for DARE [Hillman, et al. 2019]. DARE enables clinicians to feel for masses that may not be evident with direct visualization during anoscopy or HRA. Conversely, a normal DARE result does not rule out anal cancer, because it does not provide information about cytologic abnormalities, especially for superficially invasive squamous cell carcinomas (SISCCAs). In a prospective study among MSM with HIV, a palpable mass, area of induration, or ulcer was present in 85% of new cases of anal cancer; the remaining cases were SISCCAs detected solely by HRA visualization and biopsy of vascular changes [Berry, et al. 2014].

Visual examination of perianal skin and DARE are an important part of screening. Changes in sphincter tone or irregularities of the mucosa can indicate potential lesions that may need to be biopsied. All adults ≥35 years old with HIV should receive an annual DARE; DARE may be useful for diagnosing intra-anal warts in younger individuals with HIV, but anal cancer is rarely observed in these individuals. Patients with a mass felt on DARE should be referred to an experienced clinician for anoscopy and biopsy.

→ KEY POINTS

- In individuals with HIV, assessment for visible anogenital HPV lesions is part of the annual physical examination.
- If a DARE is performed with anal cytology or HRA, clinicians should obtain the cytologic sample first, before lubrication is introduced into the anal canal. Lubrication may affect the ability to obtain an adequate cytologic sample. DARE may also cause bleeding, which can contaminate the cytologic sample.

Follow-Up of Abnormal Anal Cytology Results

 anál cytology has a high sensitivity (70%), or true positive, for detection of squamous intraepithelial lesions (SIL) or the presence of any abnormality [Nathan, et al. 2010]. It has a low specificity (34%), or true negative, for high-grade SIL (HSIL) prediction in subsequent biopsy—meaning it is unable to determine that the lesion will not be high grade on histology. A cytologic result of HSIL is predictive of HSIL on biopsy (high sensitivity) [Salit, et al. 2010]. Unlike cervical cytology, a cytologic diagnosis of anal atypical squamous cells of undetermined significance (ASC-US) and low-grade SIL may have a significant risk (60% to 91%) of anal HSIL at biopsy [Darragh and Winkler 2011]. Although the appropriate follow-up for abnormal anal cytology results remains an active area of investigation, Figure 1: Follow-Up of Anal Cytologic Screening Results, below, provides a straightforward evaluative approach.

Anal human papillomavirus (HPV) screening for high-risk types, as an adjunct to anal cytology, improved identification of HSIL in a study of 894 individuals at high risk (92% men who have sex with men [MSM], 44% with HIV) [Sambursky, et al. 2018]. Addition of screening for high-risk HPV types improved the sensitivity of anal cytology to detect HSIL and may be
useful in stratifying risk among patients with benign results on anal cytology. The study showed that patients with benign anal cytology results who tested positive for high-risk HPV had a 31-fold greater risk for HSIL than those who tested negative.

**Figure 1: Follow-up of Anal Cytologic Screening Results**

<table>
<thead>
<tr>
<th>Anal cytologic screening (anal Pap test)</th>
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<tbody>
<tr>
<td>Normal cytology</td>
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<tr>
<td>Normal histology or no biopsy indicated</td>
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<tr>
<td>If positive for high-risk HPV, perform annual HRA</td>
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<tr>
<td>ASC-US</td>
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<tr>
<td>Perform HRA with biopsy if indicated</td>
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<tr>
<td>ASC-H, LSIL, or HSIL</td>
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<tr>
<td>Perform HRA with biopsy</td>
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<td>· AIN grade 1: Follow up 1 year later with HRA</td>
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<tr>
<td>· AIN grade 2/3: Treat and follow up 6 months later with HRA. Base subsequent screening and treatment on HRA results.</td>
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**Key:** AIN, anal intraepithelial neoplasia; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells cannot exclude HSIL; HPV, human papillomavirus; HRA, high resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

Abnormal anal cytology test results without abnormal histology should prompt repeat cytologic testing or HRA, if available, within 1 year to determine whether there is abnormal tissue present that corresponds to the prior screening. Because cervical and anal HPV-related dysplasia may occur at the same time, cervical cytology should be performed in individuals with HIV who have abnormal anal cytology [Kojic, et al. 2011; Gaisa M, et al. 2017].

HRA applies the techniques of standard cervical colposcopy to the examination of the anal mucosa and perianal area and is the preferred method for visualization of the anal canal in otherwise asymptomatic individuals [Berry, et al. 2004; Panther, et al. 2004]. HRA is used to obtain tissue for diagnosis.

Routine anal cytology is a standard of care in New York State for MSM, women, transgender men, and transgender women who have HIV. Clinicians and clinical sites that do not provide HRA services should establish a relationship with an experienced HRA practitioner to whom patients may be referred for follow-up. As with colposcopy, HRA is best performed by clinicians who regularly perform the procedure and understand how to evaluate abnormalities. Until a clinician develops the expertise to fully evaluate patients for abnormal anogenital physical findings, referral to an expert is indicated.

However, identification of care providers to whom patients can be referred for follow-up HRA-directed biopsy and care may be challenging. Few primary care clinicians currently have expertise in HRA, although the techniques and tools are available in many obstetric, gynecologic, colorectal, and gastrointestinal clinics, practices, and training programs. The International Anal Neoplasia Society offers an annual HRA workshop in conjunction with a colposcopy postgraduate course and has developed practice guidelines for the detection of anal cancer precursors [Hillman, et al. 2016]. Alternatively, gynecologists, nurse practitioners, and physician assistants who have experience performing cervical colposcopy can learn the techniques necessary to perform the procedure in the anus. Clinicians experienced in HRA can also train other interested clinicians outside of a formal course. The procedure should be performed regularly to maintain expertise. The UCSF Anal Cancer website has compiled a list of U.S. providers who perform HRA.
Treatment and Follow-Up

RECOMMENDATIONS: Treatment and Follow-Up

Anal High-Grade Squamous Intraepithelial Lesions (HSIL)

- Clinicians should perform post-treatment follow-up with repeat high resolution anoscopy (HRA) at 6 months in patients who have been successfully treated for anal HSIL or should refer patients for this follow-up. (A3)
- Clinicians should base follow-up after a patient’s first post-treatment HRA and biopsy based on the most recent histopathology findings (see Figure 1: Follow-up of Anal Cytologic Screening Results). (A3)

Anal Cancer

- Clinicians should immediately refer patients with a diagnosis of anal cancer to an oncologist or surgeon trained in the management of anal cancer. (A2)
- Clinicians should closely monitor patients with anal cancer in collaboration with the oncologist after definitive treatment for cancer. (A3)


Treatment and ablation of anal HSIL: Treatment of HSIL may include topical medications (e.g., topical trichloroacetic acid, imiquimod, fluorouracil [5-FU]), local destruction with infrared coagulation or electrocautery ablation, and surgical excision, which should be performed by a clinician with expertise in management of anal dysplasia. The effectiveness of treatment to prevent recurrence or disease progression remains uncertain. Follow-up with repeat HRA is recommended at 6 months post-treatment. Subsequent follow-up after the initial post-treatment HRA should be based on histopathologic findings, especially those of the most recent HRA. The most appropriate follow-up would be repeat HRA with biopsy with/without anal cytology.

Some studies have shown high rates of persistence or recurrence of HSIL after treatment with HRA and ablation [Chang, et al. 2002; Pineda, et al. 2008; Goldstone RN, et al. 2011; Gaisa MM, et al. 2020; Stier, et al. 2020]. However, the sole available randomized clinical trial that compared HSIL ablation with infrared coagulation to active monitoring (no treatment) among adults with HIV reported a significantly higher rate of complete or partial clearance of HSIL in the treatment group (82% vs. 47%) [Goldstone SE, et al. 2019]. No cases of anal carcinoma were reported among participants, possibly because of the relatively short (1-year) follow-up period.

Expectant management of HSIL: Expectant management (active monitoring) of HSIL (anal intraepithelial neoplasia [AIN] 2/AIN 3) has been proposed as an alternative to screening and treatment based on the low progression rate to squamous cell cancer (about 1.5% per year overall, 1.9% from AIN 3), the recognition of a precancerous lesion, and the high post-ablation recurrence rate of HSIL [Cajas-Monson, et al. 2018]. A large randomized clinical trial following >5,000 individuals with HIV over a 5-year period, the Anal Cancer HSIL Outcomes Research (ANCHOR) study, is currently underway to more definitively determine the benefits and risks of screening and treatment compared with expectant management to reduce the incidence of anal cancer.

Treatment for anal cancer: Treatment modalities for anal cancer may include radiation therapy, chemotherapy, excision, or combined modalities. Evidence-based recommendations on the management of anal cancer, including staging, choice of treatment, and surgical intervention, are beyond the scope of this guideline. An oncologist experienced in the management of anal cancer in individuals with HIV can address specific approaches to treatment of tumors based on size [Boman, et al. 1984; Schlienger, et al. 1989; Touboul, et al. 1994], invasiveness, and presence of residual or recurrent disease [1996; Bartelink, et al. 1997; Pocard, et al. 1998; Allal, et al. 1999].
All Recommendations

### Transmission and Prevention of HPV

- Clinicians should recommend the 9-valent human papillomavirus (HPV) vaccine 3-dose series at 0, 2, and 6 months to all individuals who are 9 to 26 [a] years of age with HIV regardless of CD4 cell count, prior cervical or anal cytology (Pap test) results, HPV test results, HPV-related cytologic changes, or other history of HPV-related lesions. (A3)
- Clinicians should engage patients who are 27 to 45 years of age in shared decision-making regarding HPV vaccination. (A3)

### Screening

- For all patients with HIV ≥35 years old, regardless of HPV vaccine status, clinicians should:
  - Inquire annually about anal symptoms, such as itching, bleeding, palpable masses or nodules, pain, tenesmus, or a feeling of rectal fullness. (A2)
  - Perform a visual inspection of the perianal [b] region. (A3)
  - Provide information about anal cancer screening and engage the patient in shared decision-making regarding screening, including anal cytology prior to digital anorectal examination (DARE). (A3)
  - Perform DARE if anal symptoms are present. (A*)
- Clinicians should promote smoking cessation for all patients with HIV, especially those at increased risk for anal cancer.
- For all patients with HIV ≥35 years old, clinicians should recommend and perform annual DARE to screen for anal pathology (B3)
- Clinicians should evaluate any patient with HIV who is <35 years old and presents with signs or symptoms that suggest anal dysplasia. (A3)
- Clinicians should conduct or refer for high resolution anoscopy (HRA) and histology (via biopsy) any patient with abnormal anal cytology. (A2)
- Clinicians should refer patients with suspected anal cancer determined by DARE or histology to an experienced specialist for evaluation and management. (A3)

### Follow-Up of Abnormal Anal Cytology Results

- Clinicians should refer patients with abnormal anal cytology results to a care provider with experience performing high resolution anoscopy (HRA) and follow up as indicated in Figure 1: Follow-Up of Anal Cytologic Screening Results. (A3)
- Clinicians should perform a cervical cytology test (Pap test) for any individual with abnormal anal cytology results who has not had negative cervical screening results within the past year. (A3)

### Anal High-Grade Squamous Intraepithelial Lesions (HSIL)

- Clinicians should perform post-treatment follow-up with repeat high resolution anoscopy (HRA) at 6 months in patients who have been successfully treated for anal HSIL or should refer patients for this follow-up. (A3)
- Clinicians should base follow-up after a patient’s first post-treatment HRA and biopsy based on the most recent histopathology findings (see Figure 1: Follow-up of Anal Cytologic Screening Results). (A3)

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a. In October 2018, the U.S. Food and Drug Administration (FDA) changed its HPV vaccination recommendations to include ages 27 to 45. There was no specific mention of HIV [U.S. FDA 2018].

b. The perianal area is a 5 cm radius from the anal verge. In women the vulvar and perianal areas overlap.
References


U.S. FDA. Vaccines, blood & biologics: Gardasil 9. 2018


