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Screening for Anal Dysplasia and Cancer in Adults With HIV

Updates, Authorship, and Related Guidelines

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Purpose of This Guideline

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 assist them in identifying opportunities for prevention, 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 by educating care providers on the importance of HPV vaccination and 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.

Because data on screening and management of anal dysplasia are limited and conflicting, many of the recommendations included here are based on the expert opinions of experienced clinicians. Results from the Anal Cancer HSIL Outcomes Research (ANCHOR) study have provided additional evidence supporting early identification and treatment of HPV-related anal disease. In the ANCHOR study, progression to anal cancer was significantly reduced in participants who received treatment for high-grade squamous intraepithelial lesions (HSILs) compared with those in the study observation arm [Palefsky, et al. 2022].

HPV-Related Anal Disease in Individuals With HIV

The American Cancer Society estimates there will be 9,440 new cases of anal cancer in 2022 among the general population in the United States: 6,290 in women and 3,150 in men [ACS 2022]. These numbers represent increases since 2020 in cases among women (6,070) men (3,020) [ACS 2021]. Human papillomavirus (HPV)-associated cancers occur more often among individuals with HIV than in the general population [Thompson, et al. 2018; Jemal, et al. 2013].

Diagnoses of anal cancer are on the rise in the United States among women in the general population; among men who have sex with men (MSM), regardless of their HIV status; and among men and women with HIV [Islami, et al. 2017; Palefsky 2017; Hessol, et al. 2013]. Incidence of squamous cell carcinoma of the anus (SCCA) is also rising in the United States, in both men and women; distant-stage SCCA incidence tripled and regional-stage SCCA incidence nearly doubled from 2001 to 2015 [Deshmukh, et al. 2020]. HIV seropositivity is associated with an increased incidence of anal cancer in both men (hazard ratio [HR], 20.73; 95% confidence interval [CI], 15.60-27.56) and women (HR, 12.88; 95% CI, 8.69-19.07) [Michaud, et al. 2020]. Current incidence rates of SCCA among MSM with HIV are higher than the rates of cervical cancer that prompted the adoption of universal screening of women for cervical dysplasia [Machalek, et al. 2012; Silverberg, et al. 2012; Gustafsson, et al. 1997].

HPV Type and Anal Dysplasia

The relationship between specific HPV types and HPV-related anal disease is still under study. It has been estimated that HPV infection is responsible for approximately 91% of anal cancers, including anal and rectal SCC [CDC 2022]. A wide range and high prevalence of HPV types responsible for oncogenic and nononcogenic HPV-related anal disease have been documented in individuals with HIV [Liu, et al. 2018; Kojic, et al. 2011; Clifford, et al. 2006]. 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 [AIDSmap 2018]. High-risk HPV types other than type 16 are more common and are more frequently associated with anal cancer among MSM with HIV than MSM without HIV [Poynten, et al. 2021]. Infection with more than 1 HPV type occurs more frequently among individuals with HIV, putting them at risk for cervical, vulvar, perianal, or anal SILs and cancer [Castilho, et al. 2015; Clifford, et al. 2006].

→ 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 SILs.

HIV and Anal Cancer Risk

HIV infection is an independent risk factor for anal HSILs [Sobhani, et al. 2004; Sobhani, et al. 2001] and confers additional risk for the development of anal cancer [Michaud, et al. 2020; Hessol, et al. 2018; Piketty, et al. 2012; Chaturvedi, et al. 2009; Shiels, et al. 2009]. Higher rates of HSILs have been documented among men and women with HIV than among the general population [Darwich, et al. 2013; Mallari, et al. 2012; Silverberg, et al. 2012].

Other risk factors associated with anal dysplasia include hepatitis B virus in MSM with HIV [Aldersley, et al. 2019], lower CD4 cell count [Baranoski, et al. 2012; Tandon, et al. 2010], and cigarette smoking [Poljak, et al. 2017; Bertisch, et al. 2013]. Some data suggest that immune reconstitution due to antiretroviral therapy reduces but does not eliminate the risk of anal cancer [Palefsky 2017; van der Snoek, et al. 2012].

HPV and Anal Dysplasia in Men

Men living with HIV, particularly MSM, have higher rates of anal HPV disease than other populations. In a multicenter cohort study, the incidence of anal cancer in MSM with HIV was 131 per 100,000 person-years, compared with 46 per 100,000 person-years in other men with HIV and 2 per 100,000 person-years in men who did not have HIV [Silverberg, et al. 2012]. In MSM with HIV, receptive anal intercourse is the most common risk factor for anal cancer, likely reflecting concurrent HPV infection.

As observed in the multicenter cohort study noted above, 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 for MSM. 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, most abnormalities were atypical squamous cells of undetermined significance. Among those with abnormal anal cytology or high-risk HPV who underwent high-resolution anoscopy, 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 the prevalence of HPV disease to guide a general screening recommendation.

HPV and Anal Dysplasia in Women

Cisgender 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 [Gandra, et al. 2015; Stier, et al. 2015; Baranoski, et al. 2012; Tandon, et al. 2010; Dal Maso, et al. 2009; Hessol, et al. 2009; Frisch, et al. 2000]. A multicenter trial reported a 27% prevalence of anal HSILs among women with HIV [Stier(b), et al. 2020].

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 [Liu, et al. 2020; Gaisa, et al. 2017; Kojic, et al. 2011], supporting the recommendation to screen all women ≥35 years old with HIV for HPV-related anal disease regardless of cervical cytology (Pap test) results (for discussion of age-based screening, see guideline section Screening for Anal Disease > Rationale for Screening).

Data are inconsistent regarding the role of anal intercourse as a risk factor for anal dysplasia in women with HIV [Stier(b), et al. 2020; Gaisa, et al. 2017; Kojic, et al. 2011; Weis, et al. 2011; Goodman, et al. 2010; Hessol, et al. 2009; Park, et al. 2009; Piketty, et al. 2003; Palefsky, et al. 2001].

→ KEY POINT

- The absence of HPV-related cervical disease in the genital tract does not eliminate the need to screen for anal dysplasia in women with HIV who are ≥35 years old.

Transgender women: Transgender women with HIV also have an increased risk of developing HPV-associated anal disease. In a recent study evaluating the anal cytology samples of 62 transgender women (69% of whom had HIV), 47% had anal dysplasia and 74% had high-risk HPV [Harfouch, et al. 2023].

Progression From Anal Dysplasia to Anal Carcinoma

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

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

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

HPV Prevention

☑ RECOMMENDATION

HPV Prevention

- Given the increased lifetime risk of persistent human papillomavirus (HPV) infection and increased prevalence of HPV-related cancers, clinicians should recommend the 9-valent HPV vaccine 3-dose series at 0, 2, and 6 months to all individuals with HIV who are 9 to 45 years old regardless of CD4 cell count, prior cervical or anal screening results, HPV test results, HPV-related cytologic changes, or other history of HPV-related lesions. (A3)

HPV Vaccine

In 2006, the U.S. Food and Drug Administration (FDA) approved a 9-valent vaccine that protects against nononcogenic 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 than other vaccines, the 9-valent vaccine is the only HPV vaccine available in the United States (see CDC: Supplemental information and guidance for vaccination providers regarding use of 9-valent HPV for more information). The HPV vaccine is approved by the FDA for preventive but not therapeutic use.

Extrapolating data from the demonstrated effectiveness of the quadrivalent HPV vaccine in older individuals [Wilkin, et al. 2018], the FDA expanded the age range for approved use of the HPV vaccine in the United States from ages 9 to 26 years to ages 9 to 45 years [FDA 2020]. There is no specific mention of HIV infection in the updated FDA approval. Although 1 study demonstrated lower efficacy of the quadrivalent vaccine in individuals with HIV [Wilkin, et al. 2018], 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 ages 9 to 12 years [CDC(a) 2021]. If possible, the HPV vaccine series should begin at 9 years old. The 3-dose vaccine is recommended for all patients with HIV who are 9 to 45 years old. 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) and should be offered regardless of CD4 cell count.

HPV vaccination provides high levels of neutralizing antibodies for at least 5 years and is protective in individuals ≤26 years old who do not have HIV, regardless of history of sexual activity; however, the full length of its protection has not been established. In an observational study conducted in England that examined the effectiveness of a national HPV immunization program, the reduction in cervical cancer was greatest in individuals who received the vaccine at ages 12 to 13 years [Falcaro, et al. 2021]. Although data are limited, the immunogenicity of the quadrivalent HPV vaccine has been demonstrated in individuals with HIV [Wilkin, et al. 2018; Kojic, et al. 2014]. In a study conducted in Italy, HPV vaccination after onset of sexual activity in men who have sex with men (MSM) <45 years old with and without HIV was associated with significantly decreased rates of squamous intraepithelial lesions (SILs). Among vaccinated participants, 54.5% with HIV and 33.3% without HIV had SILs detected, compared with 81.8% and 63.1%, respectively, of unvaccinated participants [Cavallari, et al. 2023].

Vaccination is not expected to change the course of established HPV infections but may prevent infection from other strains that are part of a polyvalent vaccine.

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]. There is no maximum interval between vaccine doses as long as 3 doses are given, so there is no need to repeat doses if a scheduled vaccination is missed [CDC(a) 2021].

Other Forms of HPV Prevention

HPV infection is the most common sexually transmitted infection (STI) in the United States, and approximately 85% of people will be infected with at least 1 HPV type during their lifetime [CDC(a) 2021; CDC(b) 2021]. Most HPV infections resolve, become latent, or are not detectable on clinical assays within a few years of exposure and infection [Ho, et al. 1998; Moscicki, et al. 1998; Evander, et al. 1995]. HPV is transmitted via skin-to-skin contact, so barrier protection, such as male/insertive and female/receptive condoms, offers 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 [Workowski and Bolan 2015].

→ KEY POINTS

- It is important that clinicians inform patients with HIV about the risk of acquiring HPV and other STIs from close physical contact with the external genitalia, anus, cervix, vagina, urethra, mouth and oral cavity, or any other location where HPV lesions are present.
- Consistent and correct condom use remains an effective way to reduce the risk of transmission of most STIs, including HPV. However, it is important that clinicians inform patients that barrier protection, such as condoms and dental dams, may not fully protect against HPV.

Screening for Anal Disease

☑ RECOMMENDATIONS

Screening for Anal Disease

- For all patients with HIV ≥35 years old, regardless of HPV vaccination 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 [a] region. (A3)
  - Provide information about anal cancer screening and engage the patient in shared decision-making regarding screening, including anal cytology before DARE. (A3)
  - Perform DARE annually and whenever anal symptoms are present. (A*)
- For adults ≥35 years old who have HIV and are men who have sex with men (A3), transgender women (A3), women (B3), or transgender men (B3), clinicians should perform or recommend annual (A3) anal Pap testing to identify potentially cancerous cytologic abnormalities.
- Clinicians should promote smoking cessation for all patients with HIV, especially those at increased risk for anal cancer. (A3)
- For all patients with HIV ≥35 years old, clinicians should recommend and perform annual DARE to screen for anal pathology. (B3)

☑ RECOMMENDATIONS

- Clinicians should evaluate any patient with HIV <35 years old who presents with signs or symptoms that suggest anal dysplasia. (A3)
- Clinicians should conduct HRA and histology (via biopsy) for any patient with LSILs or HSILs or refer as needed. (A2)
- For patients with anal cytology results indicating ASC-US, clinicians should perform HPV testing (A2):
  - If HPV testing is available and results are negative, repeat anal cytology in 1 year. (A3)
  - If HPV testing is available but reflex testing is not available, perform HPV test at follow-up within 6 months. (B2)
  - If positive for high-risk HPV or if HPV testing is not available, refer for HRA. (B2)
- Clinicians should refer patients with suspected anal cancer determined by DARE or histology to an experienced specialist for evaluation and management. (A3)
- Clinicians should discontinue screening for anal cancer when life expectancy is less than 10 years and in individuals with 2 consecutive negative anal cytology specimens who are not currently sexually active. (B3)

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; DARE, digital anorectal examination; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSILs, high-grade squamous intraepithelial lesions; LSILs, low-grade squamous intraepithelial lesions.

Note:

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

Rationale for Screening

Data on the benefit of screening and immediate treatment interventions for HPV-related anal disease are not yet definitive. However, the recently published Anal Cancer HSIL Outcomes Research (ANCHOR) study showed that treatment of HSILs significantly reduced anal cancer risk among people with HIV [Palefsky, et al. 2022]. Anal cancer screening and assessment are modeled after cervical cancer screening: early identification of SILs, follow-up to monitor for disease progression, and interventions to prevent disease progression 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 men who have sex with men (MSM), cisgender women, transgender women, and transgender men who have HIV and are ≥35 years old. 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 years. Considerations that may be weighed in the discussion include cytology results; high-risk HPV status; previously identified HSILs or atypical squamous cells, cannot exclude HSIL (ASC-H); and previous treatment.

Although this committee recommends referral to experts in HRA when indicated, the difficulty of the procedure and the training and practice required to develop expertise limit the availability of care providers for referral [Hillman(b), et al. 2016]. University of California San Francisco (UCSF) maintains a list of U.S. HRA providers, including HRA providers in New York.

→ KEY POINTS

- Inform patients about the objective of anal cancer screening and risk prevention. It is important to discuss the specifics of the screening procedure and identify patient preferences to support informed decision-making about screening [Schneiderman and Lopetegui-Lia 2020].
- Lower rates of anal cancer screening for people of color have been described and represent inequities in health care [Gillis, et al. 2020].
- Missed opportunities for screening and prevention have been documented in 44% of individuals with anal cancer [Ye, et al. 2021].

Resource: NYSDOH AI Health Equity Competencies for Health Care Providers

Anal dysplasia and invasive carcinoma are often asymptomatic. The presence of perianal warts is a risk marker for HPV type 16 infection and abnormal cytology [Cerejeira, et al. 2020]. Screening and close follow-up of individuals with HIV and HSILs

can detect preneoplastic lesions and cancers early, before clinical presentation of symptoms, and reduce mortality [Revollo, et al. 2020; Cajas-Monson, et al. 2018; Stewart, et al. 2018]. Five-year survival rates for early-stage anal cancer are much higher than for late-stage disseminated disease (81.9% vs. 34.5%) [NCI SEER 2017]. 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 the presence of HSILs [Goddard, et al. 2019]. In another prospective study of MSM with HIV and HSILs, 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 the adoption of universal screening programs. HIV infection is now recognized as an independent risk factor for anal HSILs and progression to anal cancer among MSM and women (see guideline section 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 regardless 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 HSILs in several studies [Clarke, et al. 2019; Lin, et al. 2018; Machalek, et al. 2016]; however, the high prevalence of HPV among MSM with HIV may limit 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 and Wentzensen 2018]. 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]. In a large retrospective analysis, the negative predictive value for high-risk HPV testing was 91% among MSM with and without HIV and women with HIV [Gaisa, et al. 2021].

A prospective study from Brazil confirmed the low rate of HSILs when an anal cytology result of ASC-US was associated with negative high-risk HPV, although the numbers in each subgroup limited statistical power. HSILs were present in 2 of 23 (8.7%) participants with a cytology result of ASC-US who were negative for high-risk HPV, compared with 3 of 9 (33.3%) participants with a cytology result of ASC-US and HPV type 16 or 18 [Kimura, et al. 2021]. Testing for high-risk HPV may be a useful tool for determining whether HRA is needed in patients with an anal cytology result of ASC-US.

Currently, HPV testing for anal cancer is not approved by the U.S. Food and Drug Administration and may require laboratory validation; therefore, it may not be available to all care providers.

Safety: Screening for anal cancer does have some negative effects but 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 or learning their test 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 [De-Masi, et al. 2018; Lam, et al. 2018; Ong, et al. 2018; Leeds and Fang 2016; Steele, et al. 2012].

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

→ KEY POINT

- The absence of high-risk HPV in the anal canal is associated with a low risk of high-grade dysplasia and anal cancer.

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 additional data exist, the age recommendations for screening are the same for all individuals with HIV.

Delayed diagnosis of anal cancer is common [Chiu, et al. 2015; Ristvedt, et al. 2005]. 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 old) in individuals with HIV than in those without HIV [Chiao, et al. 2008; Piketty, et al. 2008]. For individuals with HIV, this

committee recommends initiating routine anal cancer screening at age 35 due to the low incidence and low pretest probability of anal cancer in people <35 years old [Deshmukh, et al. 2017; Brickman and Palefsky 2015]. 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. Screening for anal cancer can be discontinued when life expectancy is less than 10 years and in individuals with 2 consecutive negative anal cytology specimens who are not currently sexually active.

Histopathologic Classification of Anal Cytology

Because many parallels exist between cervicovaginal and anorectal screening, the Bethesda Classification System for reporting cervical cytology terminology has been used for reporting anorectal cytology results that may require further follow-up. SILs of the anal squamous mucosa are classified as low-grade (LSILs) or high-grade (HSILs). An LSIL does not typically progress to cancer, whereas an HSIL (anal intraepithelial neoplasia [AIN] 2/AIN 3) 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).

A Pap test result of ASC-US indicates that the lesion cannot be distinguished as low-grade or high-grade. HPV genotyping is useful to stratify risk. ASC-US and ASC-H lesions require follow-up as described in the guideline section Follow-Up of Abnormal Anal Cytology Results.

Anal Cytology Tests

Baseline and annual anal cytologic screening (i.e., anal Pap testing and clinical assessment) for individuals with HIV have been suggested for many years [Rosa-Cunha, et al. 2011; Conley, et al. 2010; Palefsky, et al. 2005].

Anogenital examination to assess for visible HPV lesions is necessary because HPV can also infect the urethra and the external genitalia [Ehrenpreis and Smith 2018; Leeds and Fang 2016; Tyerman and Aboulafia 2012; Weyers, et al. 2010]. 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, 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 before cytologic screening.

Box 1: Performing an Anal Cytology Test

- Perform an anal cytology test *before* using swabs for other STI testing, using lubricant, or performing 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).
  - For detailed instructions, see University of California San Francisco Anal Cancer Information > Obtaining a specimen for anal cytology.
- 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 before 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/mm^3 and 67% when CD4 count was >400 cells/mm^3 (P=.005) [Mathews, et al. 2010]. Studies of self-collected samples for anal cytology are small and demonstrate variable reliability compared with clinician-collected samples [McNeil, et al. 2016; Cranston, et al. 2004].

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

HPV Testing

High-risk HPV is common in individuals with HIV. The absence of high-risk HPV indicates that there is no concerning dysplasia. Combining high-risk HPV testing with anal cytology facilitates the identification of patients for whom HRA can be deferred.

High-risk HPV DNA testing significantly increases sensitivity to detect high-grade dysplasia and cancer when used with anal cytology [Gaisa, et al. 2021]. A patient with a cytology result of ASC-US should be assessed for high-risk HPV in the anal canal. If high-risk HPV is present or HPV typing is not available, then HRA is indicated. If high-risk HPV is not found, then HRA can be deferred and annual screening continued [Gaisa, et al. 2021].

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, histology is required to make a diagnosis and guide interventions for anal disease (for a detailed description of this procedure, see UCSF Anal Cancer Information > DARE and HRA).

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, 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 HSILs [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 normal. 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 HSILs 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]. For cisgender men, prostate size and the presence of any nodules should be noted.

Visual examination of perianal skin and DARE are important parts of screening. Changes in sphincter tone or irregularities of the mucosa can indicate potential lesions that may require biopsy. 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 before introducing lubrication 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

☑ RECOMMENDATIONS

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 who is not up to date with current cervical screening guidelines. (A3)

Anal cytology has a sensitivity of 70% (or true positive) for detection of squamous intraepithelial lesions (SILs) or the presence of any abnormality [Nathan, et al. 2010]. It has a low specificity (34%), or true negative, for high-grade SILs (HSILs) prediction in subsequent biopsy, meaning it cannot determine that the lesion will not be high-grade on histology. A cytologic result of HSILs is predictive of HSILs 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 SILs may have a significant risk (60% to 91%) of anal HSILs at biopsy [Darragh and Winkler 2011]. Patients who do not have high-risk human papillomavirus (HPV) do not require HRA, and annual follow-up with anal cytology is appropriate for these individuals. Although the appropriate follow-up for abnormal anal cytology results remains an active area of investigation, Figure 1, below, provides a straightforward evaluative approach.

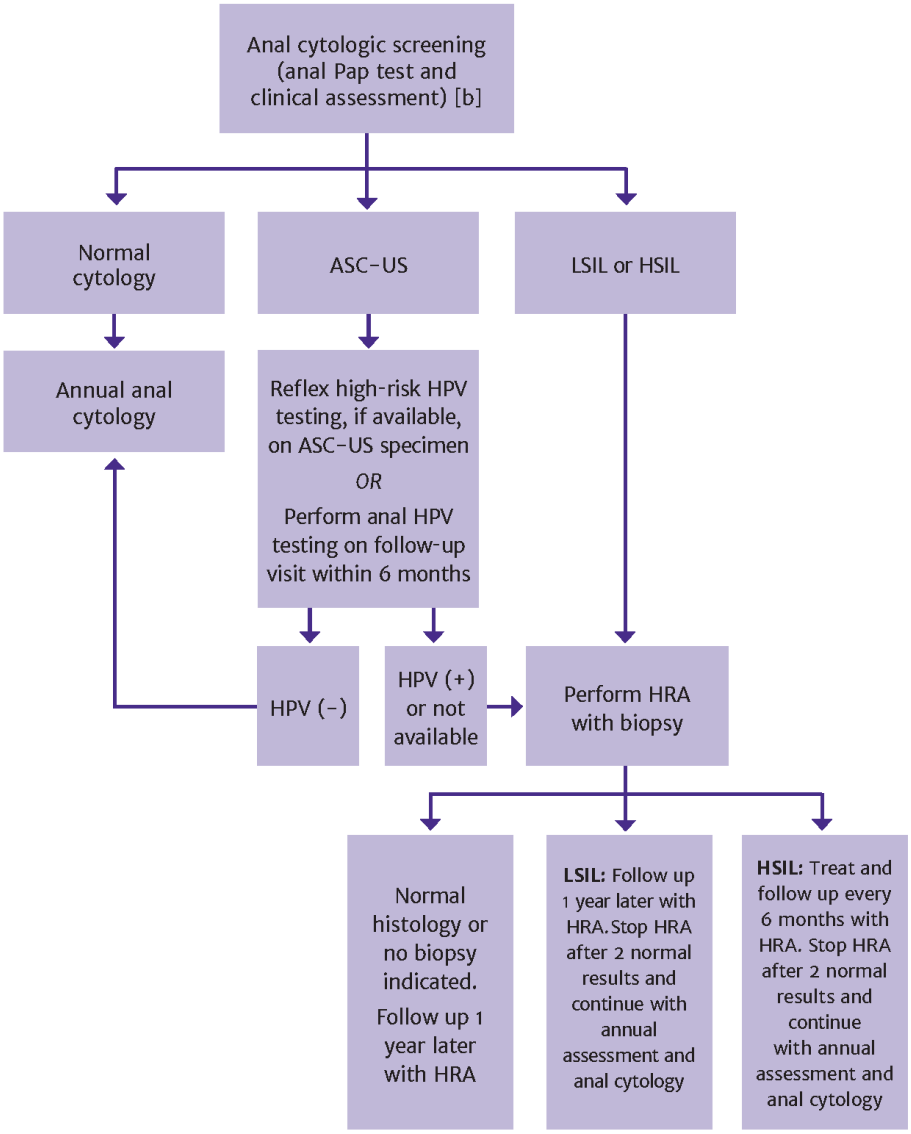
Abnormal anal cytology test results without abnormal histology should prompt repeat cytologic testing or HRA, if available, within 1 year to determine whether abnormal tissue is present that corresponds to the prior screening. Because cervical and anal HPV-related dysplasia may occur simultaneously,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

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 men who have sex with men, 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.

Identifying 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(a), 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. University of California San Francisco (UCSF) maintains a list of U.S. HRA providers, including HRA providers in New York.

Figure 1: Follow-Up of Anal Cytologic Screening Results [a]



Abbreviations: ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HRA, high resolution anoscopy, HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

Notes:

a. The figure describes recommended screening and follow-up for the following individuals with HIV who are ≥35 years old: men who have sex with men, women, transgender men, and transgender women.
b. Continued annual clinical assessment and anal cytology, with annual HRA, is recommended for patients with a history of HSILs as long as life expectancy exceeds 10 years.

Treatment and Follow-Up

☑ RECOMMENDATIONS

Anal HSILs

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

☑ RECOMMENDATIONS

- Clinicians should continue annual clinical assessment and anal cytology, with annual HRA for patients with a history of HSILs, as long as life expectancy exceeds 10 years. (A3)

Anal Cancer

- Clinicians should immediately refer patients diagnosed with 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)

Abbreviations: HRA, high-resolution anoscopy; HSILs, high-grade squamous intraepithelial lesions.

Once an HSIL has been identified, ablation is indicated. The findings of the Anal Cancer HSIL Outcomes Research (ANCHOR) study confirm that expectant management of HSILs is no longer appropriate and all HSILs should be treated.

The ANCHOR study, a randomized clinical trial that included 4,446 participants, compared treatment of HSILs with active monitoring of lesions (no treatment) in individuals with HIV ≥35 years old. The study was stopped early because of the "public health importance of the findings" [ANCHOR 2021], and the investigators found that treatment of HSILs significantly reduced the rate of progression to anal cancer by nearly 60%, with a median follow-up of 25.8 months; two-thirds of cancers were at stage I or II in trial participants [Palefsky, et al. 2022].

Treatment and ablation of anal HSILs: Treatment of HSILs may include topical medications (e.g., topical trichloroacetic acid, imiquimod, and fluorouracil), local destruction with infrared coagulation or electrocautery ablation ("hyfrecation"), and surgical excision, which should be performed by a clinician with expertise in managing anal dysplasia. Hyfrecation is generally preferred in practice. The effectiveness of treatment to prevent recurrence or disease progression remains uncertain. Follow-up with repeat HRA is recommended at 6 months post-treatment. After the initial post-treatment HRA, subsequent follow-up should be based on histopathologic findings, especially those of the most recent HRA. The most appropriate follow-up is repeat HRA with biopsy, with or without anal cytology.

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

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 [Touboul, et al. 1994; Schlienger, et al. 1989; Boman, et al. 1984], invasiveness, and presence of residual or recurrent disease [Allal, et al. 1999; Pocard, et al. 1998; Bartelink, et al. 1997].

All Recommendations

☑ ALL RECOMMENDATIONS: SCREENING FOR ANAL DYSPLASIA AND CANCER IN ADULTS WITH HIV

HPV Prevention

- Given the increased lifetime risk of persistent HPV infection and increased prevalence of HPV-related cancers, clinicians should recommend the 9-valent HPV vaccine 3-dose series at 0, 2, and 6 months to all individuals with HIV who are 9 to 45 years old regardless of CD4 cell count, prior cervical or anal screening results, HPV test results, HPV-related cytologic changes, or other history of HPV-related lesions. (A3)

Screening for Anal Disease

- For all patients with HIV ≥35 years old, regardless of HPV vaccination 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 [a] region. (A3)
  - Provide information about anal cancer screening and engage the patient in shared decision-making regarding screening, including anal cytology before DARE. (A3)
  - Perform DARE annually and whenever anal symptoms are present. (A*)
- For adults ≥35 years old who have HIV and are men who have sex with men (A3), transgender women (A3), women (B3), or transgender men (B3), clinicians should perform or recommend annual (A3) anal Pap testing to identify potentially cancerous cytologic abnormalities.
- Clinicians should promote smoking cessation for all patients with HIV, especially those at increased risk for anal cancer. (A3)
- 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 <35 years old who presents with signs or symptoms that suggest anal dysplasia. (A3)
- Clinicians should conduct HRA and histology (via biopsy) for any patient with LSILs or HSILs or refer as needed. (A2)
- For patients with anal cytology results indicating ASC-US, clinicians should perform HPV testing (A2):
  - If HPV testing is available and results are negative, repeat anal cytology in 1 year. (A3)
  - If HPV testing is available but reflex testing is not available, perform HPV test at follow-up within 6 months. (B2)
  - If positive for high-risk HPV or if HPV testing is not available, refer for HRA. (B2)
- Clinicians should refer patients with suspected anal cancer determined by DARE or histology to an experienced specialist for evaluation and management. (A3)
- Clinicians should discontinue screening for anal cancer when life expectancy is less than 10 years and in individuals with 2 consecutive negative anal cytology specimens who are not currently sexually active. (B3)

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Anal HSILs

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- Clinicians should base follow-up after a patient's first post-treatment HRA and biopsy on the most recent histopathology findings (see Figure 1: Follow-Up of Anal Cytologic Screening Results). (A3)
- Clinicians should continue annual clinical assessment and anal cytology, with annual HRA for patients with a history of HSILs, as long as life expectancy exceeds 10 years. (A3)

☑ ALL RECOMMENDATIONS: SCREENING FOR ANAL DYSPLASIA AND CANCER IN ADULTS WITH HIV

Anal Cancer

- Clinicians should immediately refer patients diagnosed with 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)

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; DARE, digital anorectal examination; HPV, human papillomavirus; HRA, high-resolution anoscopy; HSILs, high-grade squamous intraepithelial lesions; LSILs, low-grade squamous intraepithelial lesions.

Note:

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

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B. Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.