Cervical Screening for Dysplasia and Cancer

Medical Care Criteria Committee, February 2018

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Purpose of this Guideline

Medical Care Criteria Committee, February 2018

This guideline on cervical screening for individuals with HIV infection was developed by the New York State (NYS) Department of Health (DOH) AIDS Institute (AI). Its purpose is to inform primary care providers and other practitioners in NYS about cervical screening for dysplasia and cancer in eligible patients with HIV. Eligible patients include cisgender women, transgender men, and nonbinary individuals with a cervix and/or vagina. The goal of screening is to identify precancerous lesions that can be treated to prevent cervical cancer. Although the treatment approaches discussed in this guideline are based on available data on cisgender women, they are also applicable for transgender men and nonbinary individuals. This guideline addresses the following topics in cervical screening:

- Prevention, screening methods, and diagnosis and management of cervical cancer to achieve the following:
  - Increase the numbers of NYS residents with HIV infection who are screened for cervical dysplasia and whose care is managed effectively if cervical dysplasia or cancer are diagnosed.
  - Support the NYSDOH Prevention Agenda 2013–2018, which aims to increase by 5% the percentage of all females aged 21 to 65 years with an income of <$25,000 who receive cervical cancer screening [NYSDOH 2016].
  - Reduce the incidence of and morbidity and mortality associated with cervical cancer in persons living with HIV infection through early identification and treatment of precancerous and cancerous lesions, when treatment is most successful.
  - Integrate current evidence-based clinical recommendations into the healthcare-related implementation strategies of the Ending the Epidemic (ETE) initiative, which seeks to end the AIDS epidemic in NYS by the end of 2020.

KEY POINTS

- Screening for cervical cancer in the setting of HIV should be performed as detailed in this guideline for eligible individuals, including cisgender women, transgender men, and nonbinary individuals assigned female at birth. Transgender men who have an intact vagina or cervix remain at risk of human papilloma virus (HPV) infection, vaginal or cervical dysplasia, and cervical cancer [Center of Excellence for Transgender Health 2016].
- Throughout this guideline, the term transgender men refers to individuals assigned female at birth but who identify as male. Approximately one-third of transgender or gender nonconforming individuals who were assigned female at birth identify as neither male nor female (i.e., nonbinary) [James et al. 2016]. For a list of common transgender and nonbinary terms and definitions, see, for instance, UCSF Center of Excellence for Transgender Health.
- This committee encourages care providers to discuss the need for cervical cancer screening with transgender men and nonbinary individuals to help ensure appropriate care for these individuals.

Development of This Guideline

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 provided to people with HIV, hepatitis C virus, and sexually transmitted infections and to improve drug user health and LGBT health throughout the State of New York. NYSDOH AI guidelines are developed by committees of clinical experts through a consensus-driven process.
The NYSDOH AI charged the Medical Care Criteria Committee (adult HIV and related guidelines) with developing evidence-based clinical recommendations for primary care clinicians in NYS who provide gynecologic services to individuals with HIV infection. The resulting recommendations are based on an extensive review of the medical literature and reflect consensus among this panel of experts in HIV and women's health. 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 HIV Clinical Guidelines Program Recommendations Rating Scheme

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Supporting Evidence</th>
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<tbody>
<tr>
<td>A = Strong</td>
<td>1 = At least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints</td>
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<tr>
<td>B = Moderate</td>
<td>2 = One or more well-designed, nonrandomized trial or observational cohort study with long-term clinical outcomes</td>
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<tr>
<td>C = Optional</td>
<td>3 = Expert opinion</td>
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### Role of NYS Primary Care Providers

For patients with HIV infection, primary care clinicians, including mid-level care providers, have a major role in the screening, diagnosis, and treatment of gynecologic comorbidities and especially cervical dysplasia and cervical cancer. The goal of this guideline is to provide standards of care for clinicians in NYS for cervical cancer screening and follow-up in individuals with HIV infection.

### Burden of Cervical Cancer

In 2016, among all females in NYS, approximately 800 new cases of cervical cancer were diagnosed, with nearly 250 deaths from the disease [Excellus Blue Cross Blue Sheild 2017]. Females with HIV are at increased risk of HPV infection and related disease and are five times more likely to be diagnosed with cervical cancer [Grulich et al. 2007; Liu et al. 2018]. In the early years of the HIV epidemic, females with HIV infection presented with invasive cervical cancer often, had very aggressive disease with poor response to traditional therapy, and experienced a high degree of recurrence [Maiman et al. 1993a; Maiman 1993b]. In 1993, invasive cervical cancer was added as an AIDS-defining illness to underscore the need for comprehensive gynecologic evaluation in females with HIV infection [CDC. 1993]. Since then, the establishment of screening and treatment programs may partly explain the lack of a significantly increased incidence of invasive cervical cancer. Viral suppression with antiretroviral therapy may also play a role [Blitz et al. 2013]. As of February 2018, no published data are available on screening and treatment for transgender men and nonbinary individuals who have a cervix.

### References


Preventing Cervical Cancer and Precancerous Lesions
Medical Care Criteria Committee, February 2018

✓ RECOMMENDATION

HPV Vaccine
- Clinicians should recommend the 9-valent human papilloma virus (HPV) vaccine three-dose series at 0, 2, and 6 months to all individuals aged 9 to 26 years with HIV regardless of CD4 cell count, and prior cervical or anal Pap test results, HPV-related cytologic changes, or history of HPV lesions. (A3)

Nearly 100% of cervical cancers are associated with HPV infections [Winer et al. 2006; CDC 2015, 2017; Chaturvedi et al. 2011]. Although the HPV infection subtypes most commonly associated with cervical cancer are HPV 16 and HPV 18 in the general population [CDC 2015], a subgroup of approximately 13 different HPV subtypes can cause infections that result in benign condylomata acuminata (genital warts), squamous intraepithelial lesions, and cervical cancer or other anogenital carcinomas [Howlader et al. 2017]. In females living with HIV infection, a broader range of HPV oncogenic subtypes are associated with cervical dysplasia.

HPV vaccine prevents precancerous lesions: The U.S. Food and Drug Administration has approved bivalent, quadrivalent, and 9-valent HPV vaccines for young people aged 9 to 26 years, the age group in which the studies evaluating the vaccines were conducted. This age group is most likely to have an immune response to the vaccine and least likely to have already been exposed to the virus. Available data do not support HPV vaccination in adults with HIV infection who are older than 26 years [Wilkin et al. 2016]. Because of the broader coverage offered by the 9-valent HPV vaccine, it is the only HPV vaccine currently available in the United States (see the Center for Disease Control [CDC]’s HPV Vaccine for Clinicians for more information). The 9-valent vaccine protects against non-oncogenic HPV subtypes 6 and 11 and oncogenic HPV subtypes 16, 18, 31, 33, 45, 52, and 58 [FDA 2016]. Most studies indicate that the quadrivalent vaccine invokes an immune response in young people aged 9 to 26 years with HIV [Levin et al. 2017; Money et al. 2016; Denny et al. 2012]. Although the 9-valent vaccine has not been specifically studied in people living with HIV infection, it is assumed that the response will be the same in this population as with the 4-valent vaccine. It is the preferred vaccine because of the broader range of HPV subtypes seen in this population [AIDSinfo 2016; Huh et al. 2017].

Offer HPV vaccine regardless of CD4 count: HPV vaccination should be offered regardless of CD4 cell count [Kojic et al. 2014]. In the general population, a 2-dose vaccine regimen is recommended for individuals younger than 15 years, and the 3-dose vaccine regimen is recommended for individuals aged 15 years and older. For youth aged 9 to 26 years living with HIV, the 3-dose regimen remains the recommended approach [CDC 2016]. The 9-valent HPV vaccine should be administered according to the standard (CDC) schedule for immunocompromised adults and children and adolescents. In individuals who have had an abnormal Pap test result before being vaccinated, the HPV vaccine may protect against infection from HPV subtypes other than those that caused earlier or existing cervical abnormalities. See the AIDSinfo guideline on Human Papilloma Virus Disease for more information about HPV vaccination in populations with HIV [AIDSinfo 2016].

Risk of HPV-related cervical disease higher in females with HIV infection: In females with HIV infection, the risk of HPV-related cervical disease is greater than in females who do not have HIV [McKenzie et al. 2010], and cervical cancer is the leading cause of cancer death among this population [Dryden-Peterson et al. 2016]. In addition, females with HIV infection present with cervical cancer at later stages, when treatment is less successful [Maiman et al. 1993], and they have more recurrences [Huchko et al. 2014], and poorer survival rates [Dryden-Peterson et al. 2016]. These findings are most notable in females who are immune suppressed [Kreitchmann et al. 2013]. Studies also demonstrate that females with HIV infection are more likely to have abnormal cervical cytology results and that HPV DNA tests alone without cervical cytology may not adequately predict cervical abnormalities in this population [Heard 2009; Grulich et al. 2007]. However, antiretroviral therapy has a positive effect on the natural history of cervical disease in females with HIV infection by improving regression and decreasing the rate of cervical disease progression [Adler et al. 2012]. Regular cervical cytologic screening to identify precancerous lesions, coupled with treatment and follow-up, is an effective intervention for decreasing the incidence of cervical cancer [Heard 2009; Moyer 2012]. Cigarette smoking potentiates the risk for acquisition and progression of high-grade cervical intraepithelial neoplasia in females with HIV infection [Collins et al. 2010] (see NYSDOH AI Smoking Cessation Guideline).
References


Wilkin TC, Cespedes H, Paczuski M, et al. ACTG A5298: A Phase 3 Trial of the Quadrivalent HPV Vaccine in Older HIV+ Adults. CROI; 2016 Feb 22–25; Boston, Massachusetts.

Screening for Cervical Abnormalities
Medical Care Criteria Committee, February 2018

RECOMMENDATIONS

Cervical Pap Tests
- Clinicians should perform a cervical Pap test for all individuals assigned female at birth who have HIV at the following time intervals:
  - Within 2 years of the onset of sexual activity or by age 21 years. (A2)
  - Annually until 2 tests in a row screen negative, then every 3 years. (A2)
  - At 6 months after treatment for an abnormal result, then annually until 2 tests in a row screen negative, then every 3 years. (A3)
- Clinicians should perform cervical cytologic screening for individuals who have undergone a supracervical hysterectomy (cervix left in situ). (A1)
- After total hysterectomy (uterus and cervix removed), clinicians should perform vaginal Pap testing at least annually until results are negative for two tests in a row, then every 3 years. (A2)
- Clinicians should repeat cervical cytologic tests after 2 months but within 4 months after a result of “insufficient specimen for analysis.” (A3)
- Clinicians should perform HPV co-testing (cervical cytologic test with a concurrent HPV test) only for individuals who are older than 30 years. (A2)

Cervical Pap Tests
The purpose of cervical cytology (Pap test) screening is to prevent cervical cancer from developing by identifying and treating those who have abnormal cervical histology (cervical squamous intraepithelial lesions [SIL]) that increase their risk of cancer. Because the source of cervical dysplasia is genital HPV, which is a sexually transmitted infection (STI), screening before the onset of sexual debut is not useful. There are no data available to suggest a lack of risk after age 65 years. Therefore, Pap test screening for individuals with HIV who are aged 65 years and older should not be discontinued [Gravitt et al. 2013]. The Pap test is useful in identifying those who require further evaluation, which can include more frequent testing, referral for colposcopy and directed biopsy, and subsequent treatment of biopsy-proven histologic abnormalities. Although liquid-based and fixed-slide Pap test preparations are equally effective screening tools, liquid-based preparations facilitate reflex testing for HPV, the infection that causes most cervical precancerous and cancerous lesions, without requiring an additional sample.

Recent data demonstrate increased risk of anal dysplasia and rising rates of anal cancer in cisgender females with HIV. Although anal squamous intraepithelial lesions have been associated with concurrent cervical squamous intraepithelial lesions (CSIL), they also occur independently of CSIL. Therefore, anal cytology should be performed on all cisgender females with HIV [Hessol et al. 2013; Kojic et al. 2011; Gaisa et al. 2017; Stier et al. 2015] with and without cervical abnormalities according to guidelines for adults with HIV. In addition, it is important that digital examination of the anus for anal cancer and dysplasia continues at the recommended intervals. Although there are no data available on screening in transgender or nonbinary individuals with HIV, it would be logical to also perform anal screening for these populations. Digital anorectal examination (DARE), vaginal examination, and visual external anogenital examination are standard in the annual physical examination for individuals with HIV [Committee on Gynecologic Practice 2012]. DARE is a screening modality for anal cancer.

Widespread screening using cervical Pap tests has led to a decline in morbidity and mortality from cervical cancer [Howlader et al. 2017]. The benefit of cervical screening and treatment protocols for abnormalities in individuals with HIV is well established (see Cervical Pap Test Results, below, for more information).

Transgender men have lower rates of cervical screening than cisgender women. Testosterone use in transgender men is associated with high rates of inadequate Pap test results; therefore, the Pap test requisition for transgender men should note both testosterone use and the presence of amenorrhea to assist the accurate interpretation of cell morphology [Peitzmeier et al. 2014a, 2014b; TransHealth 2016]. Some transgender individuals undergo gender-
affirming treatments, including hormone therapy and/or surgeries. Genital reconstruction, such as metoidioplasty (female-to-male sex reassignment surgery) or phalloplasty to create a neopenis, may include total hysterectomy (with or without vaginectomy) or subtotal hysterectomy (cervix left in place).

Transgender women may undergo genital reconstruction, or vaginoplasty, to create a neovagina. This vaginal lining is created from penile and scrotal skin, or in some cases colon tissue. These tissues can be infected with HPV or may have other pathology. There are no studies to support cervical or vaginal screening for a neovagina; however, providers should conduct periodic visual examinations (once yearly) to evaluate for neovaginal lesions [Heller 2015; TransHealth 2016]. Asking patients to provide details about all gender-reassignment and gynecologic surgical procedures they have undergone is essential to determine the need for cervical or vaginal screening.

### KEY POINTS

- Regardless of Pap test results, it is important that routine screening for STIs continues to be performed to assess for risk behaviors that require repeat or ongoing screening.
- It is important that clinicians continue to perform visualization of the external genitalia and a digital pelvic examination as part of the annual physical examination.
- Because testosterone use can induce vaginal atrophy and affect specimen adequacy for a cervical Pap test, the Pap test requisition for transgender men should note both testosterone use and the presence of amenorrhea to assist the accurate interpretation of cell morphology [Peitzmeier et al. 2014a, 2014b; TransHealth 2016; Hembree et al. 2017]. Asking patients about all gender-reassignment and gynecologic surgical procedures is essential to determine the need for cervical or vaginal screening.

### Cervical Pap Test Results

Pap test cytology screening currently uses the Bethesda Classification System as standard nomenclature [Committee on Practice Bulletins–Gynecology 2016; Massad et al. 2013] for describing abnormal results that may require further follow-up. The Bethesda Classification System and other naming conventions (Table 2, below) describe the degree of neoplastic change found on biopsy and may still be seen in some Pap test pathology reports and in the scientific literature. These naming conventions are not interchangeable. Pap test results may include both cytological and histological nomenclature.

### Table 2. Cytological and Histological Classification of Cervical Dysplasia

<table>
<thead>
<tr>
<th>Bethesda Classification System (2014) (describes cytology obtained at cervical Pap)</th>
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<tbody>
<tr>
<td>ASC-US</td>
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<td>ASC-H</td>
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<tr>
<td>AGC</td>
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<tr>
<td>AGC-NOS</td>
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<td>AGC-FN</td>
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<td>LSIL</td>
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<td>HSIL</td>
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<td>Cancer</td>
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Table 2. Cytological and Histological Classification of Cervical Dysplasia

<table>
<thead>
<tr>
<th>Cervical Intraepithelial Lesion (or neoplasia [CIN]) (describes histology obtained at biopsy)</th>
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<tr>
<td><strong>Atypia</strong></td>
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<tr>
<td><strong>CIN I</strong> Low-grade cervical intraepithelial neoplasia</td>
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<tr>
<td><strong>CIN II</strong> Moderate-grade cervical intraepithelial neoplasia; may be a low-grade or high-grade lesion</td>
</tr>
<tr>
<td><strong>CIN III</strong> High-grade cervical intraepithelial neoplasia</td>
</tr>
<tr>
<td><strong>CIS</strong> Carcinoma in situ</td>
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<tr>
<td><strong>Cancer</strong></td>
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Adapted from Nayar et al. 2015

Pap test results can be described as atypical squamous cells (ASC) classified as “undetermined significance” (ASC-US) when the lesion cannot be determined to be high-grade (ASC-H); an ASC-H result suggests that a lesion is precancerous. Both of these lesions require follow-up as described below in the Follow-up of Abnormal Pap Test Results section.

HPV infection the primary cause of cervical cell abnormalities: Cervical squamous intraepithelial lesions (CSIL) arise at the junction of cervical squamous and columnar epithelium around the cervical os. This abnormal growth of squamous cells is the most common type of precancerous cervical lesion, causing nearly 80% of cervical cancers in all females [International Collaboration of Epidemiological Studies of Cervical Cancer 2007]. Glandular carcinoma makes up the remaining type of cervical cancer [International Collaboration of Epidemiological Studies of Cervical Cancer 2007]. CSIL occurs more frequently in females with HIV than in females without [Grulich et al. 2007; Maiman et al. 1993]. The primary cause of cervical cell abnormalities is HPV infection. HPV can be categorized as high risk (cancer causing) or low risk (benign warts) on the basis of oncogenic potential. High-risk types that are related to anogenital cancers include types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69, 70, 73, and 82 [Guan et al. 2012; Hariri et al. 2012]. Types 16 and 18 account for nearly 90% of all cervical cancers in the general population. Among females with HIV, high-risk types 51, 52, 53, 56, 58, and 59 are more common than types 16 and 18 [Hariri et al. 2012; McKenzie et al. 2010]. Of the low-risk types (6, 11, 13, 40, 42, 43, 44, 53, 54, 61, 62, 72, 73, 74, and 81), 6 and 11 are most commonly associated with benign disease (genital warts). Identifying the presence of high-risk HPV types can assist in the management of abnormal Pap test results in females with and without HIV [Hariri et al. 2012].

LSIL recurrence and progression higher in females with HIV: Low-grade squamous intraepithelial lesion (LSIL) Pap test results indicate early cell changes and possibly primary HPV infection. LSIL has demonstrated spontaneous resolution without intervention in females who do not have HIV. Data on females with HIV indicate higher rates of LSIL recurrence and progression than observed among females without HIV [Nappi et al. 2005; Robinson et al. 2003; Zeier et al. 2012]. However, there are no data currently available regarding LSIL and HPV typing. Immunocytochemistry staining of cervical cells on cytology for p16 (seen in dysplastic cervical cells but not normal cells) and Ki–67 (which can be seen in HPV–positive and HPV–negative cells) has been studied in patients without HIV [Dona et al. 2012; Solares et al. 2015; Bergeron et al. 2015; White et al. 2016; Wright et al. 2017]. The utility of this adjunctive testing on cytology is not clear. Immunocytochemistry staining has not been studied in females with HIV.

Abnormal cervical cytology requires close follow-up and referral for colposcopy: HSIL Pap test results suggest that a lesion is more likely to be precancerous. In individuals with HIV, both LSIL and HSIL require close follow-up and referral for colposcopy, which is performed as follow-up to an abnormal cytologic test or persistently positive high-risk HPV test. Colposcopy is not considered cost-effective as a primary screening test for females with or without HIV.
Glandular carcinoma of the cervix may be preceded by a negative Pap test or a test indicating the presence of atypical glandular cells (AGC) [Moukarzel et al. 2017]. AGC on a Pap test may indicate a precursor lesion for a glandular cell cervical cancer, which is rare, and also may be related to HPV infection. AGC also may be a contaminant from endometrial or fallopian tube cancer.

Abnormal cervical cytology should be followed up with colposcopy, which facilitates location of a specific lesion for biopsy and histologic diagnosis. Abnormal cytology results include an ASC-US Pap with high-risk HPV; an ASC-H, LSIL, or HSIL Pap test; or a positive high-risk HPV test in the presence of a negative or ASC-US Pap test. An AGC Pap result requires immediate follow-up with colposcopy and further evaluation. Treatment decisions are based on the resulting tissue diagnosis.

Squamous intraepithelial lesions on the vaginal cuff can be seen as recurrent disease after hysterectomy in females with a history of CSIL and as primary disease in females post-hysterectomy, not related to cervical disease [Saslow et al. 2012; Smeltzer et al. 2016]. HIV and HPV infections both increase the risk of vaginal SIL [Massad et al. 2012b]; therefore, females who have undergone a total hysterectomy for any reason should still receive annual vaginal cytologic tests [Smeltzer et al. 2016].

**HPV Testing**

HPV testing is used to identify the presence of high-risk HPV types. The presence of high-risk HPV and an abnormal Pap test indicates greater risk of precancerous disease and requires more intensive follow-up to ensure that precancerous lesions are not missed. HPV testing can also be used to help determine further management for Pap/colposcopy discrepancies in females with persistently abnormal Pap test results and negative colposcopy.

**HPV co-testing:** HPV co-testing is not indicated for individuals younger than 30 years because spontaneous clearance of HPV infection and cervical neoplasia often occur in younger females regardless of HIV status [Plummer et al. 2007; Woodman et al. 2001; Brown et al. 2005; Banura et al. 2010]. Aggressive treatment of dysplasia from transient HPV infection may damage the cervix and could be more harmful than beneficial in this age group [Bruinsma and Quinn 2011; Conner et al. 2014]. HPV co-testing (i.e., cervical cytologic test with a concurrent HPV test) has been found to be a useful adjunct to cervical cytology screening in females with HIV who are 30 years or older [Alade et al. 2017; Castle et al. 2012].

<table>
<thead>
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<th><strong>KEY POINT</strong></th>
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<td>• HPV co-testing is not recommended for individuals who are younger than 30 years.</td>
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If HPV/cervical cytologic co-testing is performed in an individual with HIV and results are positive for high-risk HPV but negative for abnormal cytology, then repeating the Pap test at a shorter interval and/or performing colposcopy may be warranted for further evaluation of abnormal cells that may have been missed initially [Keller et al. 2015]. Females with HIV, a normal Pap test, and a positive high-risk HPV test result have four times the risk of having an abnormal finding on colposcopy [Musa et al. 2014].

Data to support the safety of using HPV co-testing to extend intervals of cervical screening to every 5 years are limited to studies of females without HIV [Moyer 2012]. However, females with HIV who are taking antiretroviral therapy and have full viral suppression and a CD4 count \( \geq 500 \) cells/mm\(^3\) have cervical screening results that are comparable to females without HIV [Massad et al. 2012a; D’Souza et al. 2014]. HPV co-testing, in lieu of cervical cytology alone performed every 3 years, has been used to extend cervical cytologic screening to 5 years in females without HIV [Committee on Practice Bulletins—Gynecology 2016]. The subset of females with HIV who are virally suppressed and have a CD4 count \( \geq 500 \) cells/mm\(^3\) have the same cervical disease pathogenesis as females without HIV [Harris et al. 2005; Kim et al. 2013; Davies et al. 2015; Konopnicki et al. 2013]. When both HPV and Pap test results are negative, extension of cervical screening to every 5 years may be appropriate in individuals with HIV who have stable viral suppression and immune competence.
Conversely, individuals who present with intractable or recurrent CSIL after treatment may be demonstrating HIV progression and immune suppression. HIV viral load and CD4 cell count testing for these individuals may identify individuals who may benefit from a re-evaluation of their HIV disease treatment [Paramsothy et al. 2009].

References


Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. *BJOG* 2011;118(9):1031–41. [PMID: 21449928]


Follow-Up of Abnormal Pap Test Results

Medical Care Criteria Committee, February 2018

RECOMMENDATIONS

HPV Reflex and Co-Testing

- For individuals younger than 30 years with a cervical Pap test result of atypical squamous cells of undetermined significance (ASC-US), clinicians should ensure that a reflex human papillomavirus (HPV) test is performed. (A reflex HPV test is performed in response to, not concurrent with, an abnormal Pap test.)
  - If the reflex HPV test result is positive, clinicians should refer the patient for colposcopy. (A2)
  - If the reflex HPV test result is negative, clinicians should perform both a repeat Pap test and an HPV test at 1 year. (A2)
    - If results of both tests are negative at 1 year, then the clinician should resume standard Pap testing (every 3 years). (A2)
- For individuals 30 years or older, an HPV co-test is routinely performed along with a cervical Pap test; however, if the HPV co-test was not performed in a patient who has a Pap test result of ASC-US, then clinicians should perform HPV reflex testing.
  - If the HPV test result is positive, clinicians should refer the patient for colposcopy. (A2)
  - If the HPV test result is negative, clinicians should perform both a repeat Pap test and an HPV test at 1 year:
    - If either test result is positive, clinicians should refer the patient for colposcopy. (A2)
    - If both test results are negative, then the clinician should resume standard Pap testing (every 3 years). (A2)

Colposcopy

- For individuals of all ages, clinicians should refer for or perform colposcopy in response to the following cervical Pap test results:
  - Atypical squamous cells, HSIL cannot be excluded (ASC–H). (A1)
  - Low-grade squamous intraepithelial lesion (LSIL). (A1)
  - High-grade squamous intraepithelial lesion (HSIL). (A1)
  - Any result of atypical glandular cells (AGC). (A1)
- Colposcopy is not indicated as an initial screening test. Clinicians should limit colposcopy for use as a follow-up to abnormal screening on either Pap test or high-risk HPV test. (A2)

Repeat Cytologic Testing

- After a patient has completed treatment for an abnormal cervical biopsy test, clinicians should repeat cytologic tests at 6 months, then annually until 2 tests in a row screen negative, then every 3 years. (A3)

Because an ASC–US Pap test result indicates the inability to determine whether the cellular abnormality is benign or high risk, an HPV test in response to the Pap result (HPV reflex testing) should be performed regardless of a patient's age to identify possible high-risk HPV infection, which, if present, requires follow-up with colposcopy.

Colposcopy with biopsy is the diagnostic test for cervical dysplasia that is identified through the screening Pap test. It should not be used as a primary screening test. Colposcopy is used to visualize abnormal cervical tissue suggestive of precancerous lesions. It is also used to obtain a directed (by visualization) biopsy for a histological specimen, which has better sensitivity and specificity for SIL than cytology alone. Random biopsies are not useful for cervical diagnosis. Although a simple cervical biopsy has not been associated with increased vaginal shedding of HIV [ACOG 2013], one study found an association between loop electrosurgical excision, a procedure used to biopsy or fully excise a lesion and provide a specimen for diagnosis, and increased viral shedding [Huchko et al. 2013]. Cryotherapy, used for treatment by ablating the lesion, does not increase cervical HIV viral shedding [Chung et al. 2011]. It is important that clinicians help patients understand the need to use effective barrier protection during sexual activity until healing is complete after this procedure [Lam 2014].
FIGURE 1. Follow-Up for Cervical Pap Test Result Atypical Squamous Cells of Undetermined Significance (ASC-US) in Individuals with HIV Infection

*HPV co-testing versus reflex testing: HPV co-testing is routinely performed at the same time as a cervical Pap test in individuals 30 years or older. HPV reflex testing is performed in response to an abnormal cervical Pap test result in individuals younger than 30 years, and in individuals 30 years or older who did not receive an HPV co-test at the time of their cervical Pap test.
References
Diagnosed Cervical Cancer

Medical Care Criteria Committee, February 2018

RECOMMENDATIONS

When Cervical Cancer is Diagnosed

- Clinicians should immediately refer patients with HIV infection and a diagnosis of cervical cancer to a gynecologic oncologist or surgeon trained in the management of cervical cancer. (A2)
- Clinicians should closely monitor patients with cervical cancer in close collaboration with the gynecologic oncologist after definitive treatment for cancer. (A3)

Patients with cervical cancer may have few and nonspecific symptoms; when they do present with symptoms, more advanced disease is often found. Vaginal bleeding and post-coital bleeding are the most common symptoms. Malodorous vaginal discharge, pelvic pain, back pain, and lower abdominal pain are also common. Weight loss, leg pain, edema, and obstructive uropathy indicate advanced disease [American Cancer Society 2016]. Patients with a diagnosis of cervical cancer, with or without symptoms, should be referred immediately for assessment and management of their disease. Support services are often effective in facilitating patient engagement and maintenance in cancer treatment and care.

The standard therapeutic approach to treating cervical cancer in individuals with HIV infection is the same as that for individuals without HIV infection. Research suggests that patients have better survival outcomes when treated by gynecologic oncology specialists [Mercado et al. 2010]. Appropriate staging, management, and therapy for cervical cancer should be determined by a gynecologic oncologist or a clinician with similar training and experience [Mercado et al. 2010; Bristow et al. 2004]. Management and therapy should be based on the stage of disease. Treatment may include cone biopsy/loop electrosurgical excision procedure, total hysterectomy, radical hysterectomy, radiation therapy, chemotherapy, and combined modality therapy with surgery, radiation, and chemotherapy. The increased risk of treatment failure and high recurrence rate in individuals with HIV infection demand close follow-up by a multidisciplinary team of clinicians even after definitive treatment for cervical cancer.

References


All Recommendations

HPV Vaccine
- Clinicians should recommend the 9-valent human papilloma virus (HPV) vaccine three-dose series at 0, 2, and 6 months to all individuals aged 9 to 26 years with HIV regardless of CD4 cell count, and prior cervical or anal Pap test results, HPV-related cytologic changes, or history of HPV lesions. (A3)

Cervical Pap Tests
- Clinicians should perform a cervical Pap test for all individuals assigned female at birth who have HIV at the following time intervals:
  - Within 2 years of the onset of sexual activity or by age 21 years. (A2)
  - Annually until 2 tests in a row screen negative, then every 3 years. (A2)
  - At 6 months after treatment for an abnormal result, then annually until 2 tests in a row screen negative, then every 3 years. (A3)
- Clinicians should perform cervical cytologic screening for individuals who have undergone a supracervical hysterectomy (cervix left in situ). (A1)
- After total hysterectomy (uterus and cervix removed), clinicians should perform vaginal Pap testing at least annually until results are negative for two tests in a row, then every 3 years. (A2)
- Clinicians should repeat cervical cytologic tests after 2 months but within 4 months after a result of "insufficient specimen for analysis." (A3)
- Clinicians should perform HPV co-testing (cervical cytologic test with a concurrent HPV test) only for individuals who are older than 30 years. (A2)

HPV Reflex and Co-Testing
- For individuals younger than 30 years with a cervical Pap test result of atypical squamous cells of undetermined significance (ASC-US), clinicians should ensure that a reflex human papillomavirus (HPV) test is performed. (A reflex HPV test is performed in response to, not concurrent with, an abnormal Pap test.)
  - If the reflex HPV test result is positive, clinicians should refer the patient for colposcopy. (A2)
  - If the reflex HPV test result is negative, clinicians should perform both a repeat Pap test and an HPV test at 1 year. (A2)
    - If results of both tests are negative at 1 year, then the clinician should resume standard Pap testing (every 3 years). (A2)
- For individuals 30 years or older, an HPV co-test is routinely performed along with a cervical Pap test; however, if the HPV co-test was not performed in a patient who has a Pap test result of ASC-US, then clinicians should perform HPV reflex testing.
  - If the HPV test result is positive, clinicians should refer the patient for colposcopy. (A2)
  - If the HPV test result is negative, clinicians should perform both a repeat Pap test and an HPV test at 1 year:
    - If either test result is positive, clinicians should refer the patient for colposcopy. (A2)
    - If both test results are negative, then the clinician should resume standard Pap testing (every 3 years). (A2)

Colposcopy
- For individuals of all ages, clinicians should refer for or perform colposcopy in response to the following cervical Pap test results:
  - Atypical squamous cells, HSIL cannot be excluded (ASC-H). (A1)
  - Low-grade squamous intraepithelial lesion (LSIL). (A1)
  - High-grade squamous intraepithelial lesion (HSIL). (A1)
  - Any result of atypical glandular cells (AGC). (A1)
- Colposcopy is not indicated as an initial screening test. Clinicians should limit colposcopy for use as a follow-up to abnormal screening on either Pap test or high-risk HPV test. (A2)
Repeat Cytologic Testing

- After a patient has completed treatment for an abnormal cervical biopsy test, clinicians should repeat cytologic tests at 6 months, then annually until 2 tests in a row screen negative, then every 3 years. (A3)

When Cervical Cancer is Diagnosed

- Clinicians should immediately refer patients with HIV infection and a diagnosis of cervical cancer to a gynecologic oncologist or surgeon trained in the management of cervical cancer. (A2)
- Clinicians should closely monitor patients with cervical cancer in close collaboration with the gynecologic oncologist after definitive treatment for cancer. (A3)
How This Guideline Was Developed

Medical Care Criteria Committee (see below), February 2018

The New York State Department of Health (NYSDOH) AIDS Institute (AI) protects and promotes the health of New York State's diverse population through disease surveillance and the provision of quality services for prevention, health care, and psychosocial support for those affected by HIV/AIDS, sexually transmitted infections, viral hepatitis, and related health concerns. In addition, the NYSDOH AI promotes the health of LGBT populations, substance users, and the sexual health of all New Yorkers.

Medical Care Criteria Committee for Adult HIV Care Guidelines

The NYSDOH AI charged the Medical Care Criteria Committee (adult HIV and related guidelines) with developing evidence-based clinical recommendations for primary care clinicians in NYS who provide gynecologic services to individuals with HIV infection. The purpose of the Cervical Screening for Dysplasia and Cancer clinical practice guideline is to inform primary care providers and other practitioners in NYS about cervical screening for dysplasia and cancer in cisgender women, transgender men, and nonbinary individuals assigned female at birth with an intact vagina or cervix, with the goal of identifying precancerous lesions that can be treated to prevent cervical cancer.

Committee Makeup: Members of the MCCC (see Box A1: MCCC Leaders, Members, and Cervical Screening Guideline Reviewers, below) were appointed by the NYSDOH AI to ensure representation of clinical practice in all major regions of the state, relevant medical disciplines and sub-specialties, key NYS agencies, community stakeholders, and patient advocates. Individuals confirmed as Committee members are required to disclose any potential conflicts of interest; disclosures are reviewed and approved by the NYSDOH AIDS Institute Office of the Medical Director (see Funding and Financial Disclosure of Potential Conflicts of Interest, below).

Committee Role: Committee members actively participate in guideline development, including evidence review, drafting of recommendations and text, manuscript review, consensus approval of all recommendations, and rating of recommendations.

Committee Leadership: Working with the lead author, the MCCC Planning Group of Committee leaders reviewed and refined the manuscript, facilitated consensus approval of all recommendations, and addressed feedback from external peer and consumer reviewers.

Johns Hopkins University (JHU) Editorial Role: The JHU editorial team coordinated, guided, and documented all Committee activities, and edited the guideline material for clarity, flow, and style.

MCCC Planning Group (all Committee members and reviewers are listed in Box C1, below)
- Samuel T. Merrick, MD, Chair
- Joseph P. McGowan, MD, FACP, FIDSA, Vice-Chair
- Judith A. Aberg, MD, FIDSA, FACP, Chair Emeritus
- Gina M. Brown, MD, Bethesda, MD (Medical Officer, Office of AIDS Research, National Institutes of Health)
- Charles J. Gonzalez, MD, AIDS Institute Associate Medical Director for Science and Policy
- Christopher J. Hoffmann, MD, MPH, JHU Principal Investigator

AIDS Institute and JHU Editorial and Program Management Team
- Laura Duggan Russell, MPH, AIDS Institute Guidelines Program Coordinator
- Mary Beth Hansen, MA, JHU Guidelines Project Director
- Christina Norwood, MS, ELS, JHU Senior Editor
- Johanna Gribble, MA, JHU Medical Editor
- Jen Ham, MPH, JHU Medical Editor
- Jesse Ciekot, JHU Program Coordinator
Box A1: MCCC Leaders and Members (when this guideline was developed), and Cervical Screening Guideline External Reviewers

Leadership
- **Chair:** Samuel T. Merrick, MD, New York Presbyterian–Weill Cornell, New York, NY
- **Vice-Chair:** Joseph P. McGowan, MD, FACP, FIDSA, North Shore University Hospital, Manhasset, NY
- Chair Emeritus: Judith A. Aberg, MD, FIDSA, FACP, Icahn School of Medicine at Mount Sinai, New York, NY
- **Medical Director:** Bruce D. Agins, MD, MPH, New York State Department of Health (NYSDOH) AIDS Institute (AI), New York, NY (retired as of October 30, 2017)
- **Deputy Medical Director:** Lyn Stevens, MS, NP, ACRN, New York State Department of Health (NYSDOH) AIDS Institute (AI), Albany, NY
- **JHU Principal Investigator:** Christopher J. Hoffmann, MD, MPH, Johns Hopkins University School of Medicine, Baltimore, MD

Contributing Members and Liaisons
- Sheldon T. Brown, MD, James J. Peters Veterans Affairs Medical Center, Bronx, NY (Liaison for NYS Department of Veterans Affairs Medical Center)
- James C.M. Brust, MD, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY
- Demetre Daskalakis, MD, MPH, Long Island City, NY (New York City Department of Health and Mental Hygiene Liaison)
- Elliot DeHaan, MD, Stony Brook University Medical Center, East Setauket, NY
- Steven M. Fine, MD, PhD, University of Rochester Medical Center, Rochester, NY
- Douglas G. Fish, MD, NYSDOH, Albany, NY (Liaison for NYSDOH Office of Health Insurance Programs)
- Jack Fuhrer, MD, Stony Brook University Medical Center, East Setauket, NY
- Charles J. Gonzalez, MD, New York, NY (Clinical Liaison for NYSDOH AIDS Institute)
- Peter G. Gordon, MD, Columbia University College of Physicians and Surgeons, New York, NY (Liaison for NYSDOH AI HIV Quality of Care Advisory Committee)
- Annette Gaudino, Treatment Action Group (Liaison for TAG), New York, NY
- Christine A. Kerr, MD, Hudson River HealthCare, Beacon, NY
- Carl J. Koenigsmann, MD, NYS DOCCS, Albany, NY (Liaison for NYS Department of Corrections and Community Supervision)
- Luz Amarilis Lugo, MD, Mount Sinai Comprehensive Health Program–Downtown, New York, NY
- Cynthia H. Miller, MD, Albany Medical College, Albany, NY
- Gene Morse, PharmD, FCCP, BCPS, University at Buffalo, Buffalo, NY
- Julie E. Myers, MD, MPH, New York City (NYC) Department of Health and Mental Hygiene (DOHMH), Long Island City, NY (Liaison for NYC DOHMH)
- David C. Perlman, MD, Mount Sinai Beth Israel, New York, NY
- Carlos Salama, MD, Elmhurst Hospital Center, Elmhurst, NY (Liaison for New York City Health + Hospitals)
- Noga Shalev, MD, Columbia University Medical Center, New York, New York
- Cheryl A. Smith, MD, AIDS Institute, New York, NY (Liaison for NYSDOH AI Clinical Education Initiative)
- Antonio E. Urbina, MD, Mount Sinai St Luke’s, New York, NY (Liaison for NYSDOH AI Clinical Education Initiative)
- Rona M. Vail, MD, Callen-Lorde Community Health Center, New York, NY
- William M. Valenti, MD, FIDSA, Trillium Health, Rochester, NY (Liaison for the Medical Society of the State of New York)

Expert Consultants and Contributors
- Joel Palefsky, MD, University of California, San Francisco School of Medicine
- Asa Radix, MD, MPH, FACP, Callen–Lorde Community Health Center
- Tim Wilkin, MD, Weill Cornell Medical College

Expert Consultants and Contributors
- Gregg Alleyne, MD, FACOG, Drexel University College of Medicine
- John Clark, MD, ABOG, Columbia University
Funding and Disclosure of Potential Conflicts of Interest (COIs)

**Funding:** New York State funds supported development of the *Cervical Screening for Dysplasia and Cancer in the Setting of HIV* guideline through a grant awarded to the Johns Hopkins University School of Medicine, Division of Infectious Diseases, from the New York State Department of Health AIDS Institute.

**Conflicts of interest:** All active MCCC members, invited consultants and coauthors, peer reviewers, and program staff are required to disclose financial relationships with commercial entities, including gifts that may be actual conflicts of interest or may be perceived as conflicts. These individuals must disclose financial relationships annually, for themselves, their partners/spouses, and their organization/institution. On their annual disclosures, MCCC members are asked to report for the previous 12 months and the upcoming 12 months. Box A2, below, lists reported conflicts.

**Management of COIs:** All reported financial relationships with commercial entities are reviewed by the NYSDOH AI guidelines program to assess the potential for undue influence on guideline recommendations made by the Committee. For the Committee members reporting conflicts, it was determined that because there is just one HPV vaccine available in the United States, the potential for exertion of undue influence on recommendations was exceedingly low to non-existent.

All guideline recommendations received consensus approval of the full MCCC, and the final review and approval of the recommendations was performed by the Committee Chair, and the NYSDOH AI Medical Director and Deputy Medical Director, none of whom reported conflicts of interest.

External peer reviewers were also required to submit conflict of interest/financial disclosure information, which were similarly screened. Neither peer reviewer reported conflicts.

**Box A2: Reported Conflicts of Interest/Financial Disclosure Results**

<table>
<thead>
<tr>
<th>Committee/Guideline Role</th>
<th>Relationships disclosed for the previous and/or upcoming 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning Group Member</td>
<td>Research support: Gilead, ViiV Healthcare; scientific advisor: Merck</td>
</tr>
<tr>
<td>Planning Group Member</td>
<td>Scientific advisor: Merck</td>
</tr>
<tr>
<td>Committee Member</td>
<td>Scientific advisor: GFORCE</td>
</tr>
<tr>
<td>Committee Member</td>
<td>Consultant: Roche Diagnostics</td>
</tr>
<tr>
<td>Committee Member</td>
<td>Consultant: Gilead, Merck, ViiV, BMS</td>
</tr>
<tr>
<td>Expert Consultant</td>
<td>Research support: Antiva, Ubiome, Agenovir Scientific advisor: Merck, Ubiome, Antiva, Agenovir</td>
</tr>
</tbody>
</table>
Evidence Collection and Review

The NYSDOH AI guideline development process is based on a strategic search and analysis of the published evidence. Box A3 illustrates the evidence review and selection process.

<table>
<thead>
<tr>
<th>Box A3: Evidence Collection and Review Processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NYSDOH AI and MCCC defined the goal of the guideline: To provide evidence-based clinical recommendations for the management of cervical screening for dysplasia and cancer in females with HIV infection.</td>
</tr>
<tr>
<td>• MCCC appointed a lead author, who conducted a systematic literature search in PubMed using MESH terms. All searches were limited to studies that 1) were published within the previous 5 years; 2) involved only human subjects; and 3) were published in English.</td>
</tr>
<tr>
<td>• Lead author reviewed studies identified through searches, and excluded based on the following criteria:</td>
</tr>
<tr>
<td>▪ Based on publication type, study design, participants and clinical relevance to the guideline.</td>
</tr>
<tr>
<td>▪ Author and editorial staff conducted additional searches using PubMed and online databases to identify:</td>
</tr>
<tr>
<td>▫ Studies published prior to the 5-year search limit</td>
</tr>
<tr>
<td>▫ Studies published during the guideline development process</td>
</tr>
<tr>
<td>▫ Recent conference abstracts</td>
</tr>
<tr>
<td>▫ Older studies known to provide strong evidence in support of specific recommendations or to undergird expert opinion</td>
</tr>
<tr>
<td>▫ New York State epidemiologic data</td>
</tr>
<tr>
<td>• Lead author developed and all MCCC members reviewed and approved evidence-based guideline recommendations:</td>
</tr>
<tr>
<td>▪ Planning group reviewed, deliberated, refined, and approved draft recommendations.</td>
</tr>
<tr>
<td>▪ MCCC members reviewed, provided written comment on, deliberated, and reached consensus on recommendations</td>
</tr>
<tr>
<td>▪ Planning group reviewed the cited evidence and assigned a two-part rating to each recommendation to indicate the strength of the recommendation and the quality of the supporting evidence; consensus reached on ratings.</td>
</tr>
<tr>
<td>▫ Additional evidence identified and cited during the rating process (see Box C4, below)</td>
</tr>
<tr>
<td>• Ongoing update process</td>
</tr>
<tr>
<td>▪ JHU editorial staff will surveil published literature on an ongoing basis to identify new evidence that may prompt changes to existing recommendations or development of new recommendations</td>
</tr>
<tr>
<td>▪ JHU editorial staff will ensure that the MCCC reviews new studies at least four times per year, and more often if newly published studies, new drug approval, or drug-related warning indicate the need for an immediate change to the published guideline.</td>
</tr>
<tr>
<td>▪ JHU editorial staff will track, summarize, and publish ongoing changes to the guideline</td>
</tr>
<tr>
<td>▪ MCCC reviews and approves substantive changes to, additions to, or deletions of recommendations</td>
</tr>
<tr>
<td>▪ The Committee will initiate a full review of the guideline 4 years after the original publication date</td>
</tr>
<tr>
<td>• NYSDOH AI will publish a comprehensive update 5 years after the original publication date</td>
</tr>
</tbody>
</table>
Recommendation Development and Rating Process

The clinical recommendations presented in this guideline were developed by consensus based on a synthesis of the current evidence collected through the systematic search described above. If no data were available, the recommendations are based on expert opinion, and this status is indicated in the rating and in the text.

The Planning Group met via monthly teleconferences over approximately 24 months to finalize the guideline and reach consensus on recommendations and rationale. Once consensus among the Planning Group members was reached, the guideline was reviewed by the full MCCC, and consensus was reached on all recommendations. These deliberations were conducted by teleconference; MCCC members were invited to submit comments in writing as well. Committee review discussions were recorded, and recordings were reviewed carefully to ensure that all decisions and changes were captured and integrated into the manuscript.

Members of the Planning Group then individually reviewed the evidence for each recommendation and assigned a two-part rating (see below). The individual ratings were compiled into a report distributed to all raters, and conference call discussions were held to deliberate ratings for which consensus was needed. Once all raters agreed on the interpretation of evidence and ratings for all recommendations, the guideline was sent to the NYSDOH AI for review and approval.

| AIDS Institute HIV Clinical Guidelines Program Recommendations Rating Scheme |
|----------------------------------|----------------------------------|
| **Strength of Recommendation**   | **Quality of Supporting Evidence** |
| A = Strong                       | 1 = At least 1 randomized trial with clinical outcomes and/or validated laboratory endpoints |
| B = Moderate                     | 2 = One or more well-designed, nonrandomized trial or observational cohort study with long-term clinical outcomes |
| C = Optional                     | 3 = Expert opinion |

External Review

Two external peer reviewers recognized for their experience and expertise in HIV care were identified by program leaders (see Box A1). These individuals submitted a financial disclosure statement for the purpose of identifying potential conflicts of interest before participating as peer reviewers; neither disclosed financial relationships with commercial entities in the 12 months prior or the 12 months following submission of the disclosure.

Peer reviewers were asked to review the guideline for accuracy, balance, clarity, and practicality of the recommendations for primary care providers. The Planning Group addressed peer review feedback; any conflicting opinions were resolved by the Committee chairs. Members of NYSDOH AI Community Advisory Committee also reviewed and commented on the guideline.

Guideline Updates

Members of the MCCC will monitor developments in cervical screening in an ongoing structured manner to maintain guideline currency. Once the guidelines are published on the program website: www.hivguidelines.org, any updates will be made to the HTML document as needed as new peer reviewed literature on cervical screening in general and in the setting of HIV infection specifically is published.

Notification of newly published studies will be automated, and the Planning Group will review new data at least every 4 months. Newly published data that provide support for existing recommendations will be cited in the text, and the studies will be added to the reference list(s).
If newly published data prompt a revision to recommendations or rationale, the Planning Group will propose appropriate edits and determine whether the changes warrant review and approval by the entire MCCC. If MCCC review is required, a conference call will be convened for that purpose. Deletion of existing recommendations, addition of any new recommendations, and/or substantive changes to existing recommendations will prompt MCCC review and consensus.

If a new medication or formulation is approved, the Planning Group will be convened via conference call to examine the data, consider inclusion in the guideline, and determine the need for MCCC review and approval.

The full guideline will be reviewed and updated on the 4th anniversary of original publication to prepare for publication of an updated guideline on or before the 5th anniversary of original publication.