



CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Human Papillomavirus (HPV) in Patients with HIV

Medical Care Criteria Committee, July 2018

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Human Papillomavirus (HPV) in Patients with HIV

Purpose of This Guideline

Medical Care Criteria Committee, July 2018

This guideline on human papillomavirus (HPV) in individuals with HIV 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 HPV-related cervical and anal disease and to identify opportunities for screening and treatment. Accordingly, this guideline addresses the following topics on HPV: prevention, screening methods, diagnosis and presentation, and treatment. This guideline aims to achieve the following goals:

- Increase the numbers of NYS residents with HIV who are screened for HPV-related dysplasia and provided with effective care for HPV-related disease.
- Support the NYSDOH Prevention Agenda 2013–2018 to decrease the burden of HPV by educating providers on the importance of HPV vaccination and increasing the three-dose HPV immunization rate [NYSDOH 2016].
- Reduce the morbidity and mortality associated with HPV in people with HIV through early identification and treatment of precancerous and cancerous lesions, when treatment is most likely to be successful.
- Integrate current evidence-based clinical recommendations into the healthcare-related implementation strategies of the Ending the Epidemic initiative, which seeks to end the AIDS epidemic in New York State by the end of 2020.

The Burden of HPV

There are many HPV types, some of which cause cancer (oncogenic) and others that cause noncancerous disease (non-oncogenic verruca vulgaris and condyloma acuminata). A subgroup of approximately 30 different HPV types infects cells in the anus and genital tract, including the cervix, and may cause asymptomatic infection, condylomata acuminata (genital warts), squamous intraepithelial lesions (SIL), glandular cell abnormalities, and, rarely, anal and cervical cancer or other genital carcinomas. The incidence of HPV-related oropharyngeal cancer is increasing [CDC 2017a–d]. HPV infection is often asymptomatic, and the time course from initial infection to the presence of lesions has not been determined. These factors prevent a reliable method for determining the source and time of acquisition.

In the general U.S. population, HPV types 16 and 18 are responsible for approximately 70% of cases of cervical and anal SIL and cervical and anal cancers [Steinbrook 2006; Lowy and Schiller 2012] in addition to most oropharyngeal, vaginal, vulvar, and penile cancers [Bouvard et al. 2009; Grulich et al. 2010; Forman et al. 2012; Saraiya et al. 2015]. Non-oncogenic HPV types 6 and 11 account for approximately 90% of genital warts [Steinbrook 2006]. A wider range and higher prevalence of HPV types responsible for oncogenic and non-oncogenic disease have been documented in people with HIV [Clifford et al. 2006; Kojic et al. 2011; Massad et al. 2016]. HPV-associated cancers occur more often among people with HIV and AIDS than in the general population [Jemal et al. 2013; Liu et al. 2018]. The distribution of HPV types responsible for SIL and warts also differs between these two populations [Clifford et al. 2006]. HPV type 16 is the most common high-risk type associated with cervical, anal, and penile neoplasia. HPV types 58 and 52 also are frequently associated with cervical SIL in women with HIV but are rarely associated with SIL in women without HIV [Clifford et al. 2006]. Although HPV type 18 is commonly associated with SIL in individuals without HIV, it is much less common in people with HIV [Clifford et al. 2006]. Infection with more than one HPV type occurs more frequently among individuals with HIV, and these individuals can be at risk of cervical and/or anal SIL and nonmalignant disease simultaneously [Clifford et al. 2006; Castilho et al. 2015].

Tobacco use is an established contributor to HPV's oncogenic potential and is an independent risk factor for acquisition and progression of cervical SIL [Collins et al. 2010], anal neoplasia [Daling et al. 2004], oropharyngeal

cancer [NCI 2018], and vulvar cancer in individuals with HIV [Kutlubay et al. 2013; ACS 2018]. Some data suggest that HIV-related immune suppression can contribute to relapse and progression of HPV disease, and antiretroviral therapy-mediated immune reconstitution can lead to regression of SIL associated with HPV infection [Blitz et al. 2013]. Other studies do not support this finding [Adler 2010; Piketty et al. 2013].

Cervical cancer rates have decreased due to the benefit of a robust screening system in the United States that has been in place since the 1960s. The incidence of anal cancer persists, particularly among men who have sex with men with and without HIV and among women with HIV [Palefsky et al. 1998; Clifford et al. 2005; Diamond et al. 2005; Hessol et al. 2009, 2013; Islami et al. 2017]. Screening for anal HPV disease is a relatively new recommendation, and data on the benefit of screening and immediate treatment interventions are not yet definitive. Based in part on the epidemiological evidence and benefits of the analogous cervical screening, this Committee has recommended anal screening for individuals with HIV since 2007. Studies are underway to clarify the benefit of immediate treatment interventions for anal HPV disease [AMC 2017]. Although screening tests are available for oropharyngeal cancers, the utility and benefits have not been established; therefore screening other than visual inspection, is not yet recommended [see *American Dental Association > Oral and Pharyngeal Cancer* for more information]. There are no routine screening tests or procedures for vulvar, vaginal, or penile cancers.

The Role of Primary Care Providers in New York State

Primary care clinicians have a major role in the prevention, screening, diagnosis, and treatment of sexually transmitted infections in individuals with HIV. The goal of this guideline is to provide standards for clinicians in NYS to prevent and identify HPV disease and to determine appropriate treatment and follow-up in individuals with HIV.

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 NYS. 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 services to individuals with HIV. 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	
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

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Transmission and Prevention

Medical Care Criteria Committee, July 2018

✓ RECOMMENDATIONS

Transmission and Prevention

- Clinicians should recommend the 9-valent human papillomavirus (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, prior cervical or anal Pap test results, HPV-related cytologic changes, or history of HPV lesions. (A3)
- Clinicians should inform patients with HIV about the risk of acquiring HPV and other sexually transmitted infections (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. (A3)

HPV Vaccine

The U.S. Food and Drug Administration (FDA) has approved bivalent (Cervarix), quadrivalent (Gardasil), and 9-valent (Gardasil-9) 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 least likely to have been previously exposed to HPV and more likely to have an immune response to the vaccine. HPV vaccination may be scheduled at the same time as the standard adolescent vaccines offered at age 11 to 12 years. For young people who have experienced sexual abuse or assault or who are immune compromised, the vaccine series should begin at age 9 years [CDC 2018]. Available data do not support HPV vaccination in adults older than 26 years, including those with HIV [Wilkin et al. 2016]. Mathematical modeling based on the quadrivalent vaccine has demonstrated that offering HPV vaccination to HIV-infected men who have sex with men up to age 40 years likely would be cost-effective [Lin et al. 2017]; however, this study did not account for lower vaccine response rates with increased age. Other analyses demonstrate efficacy, although at rates lower than in adolescents; a comparable immune response for HPV 16; and a slightly lower immune response for HPV types 6, 11, and 18 among women aged 25 to 45 years [Munoz et al. 2009; Westra et al. 2011]. The bivalent vaccine protects against oncogenic types 16 and 18, and the quadrivalent vaccine (Gardasil) protects against HPV non-oncogenic types 6 and 11 in addition to oncogenic types 16 and 18. The 9-valent vaccine (Gardasil-9) protects against non-oncogenic HPV types 6 and 11 and oncogenic HPV types 16, 18, 31, 33, 45, 52, and 58. 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 Centers for Disease Control and Prevention [CDC] *HPV Vaccine Information for Clinicians* for more information). The HPV vaccine is FDA-approved for preventive but not therapeutic use; there are no data to support the use of the HPV vaccine to ameliorate existing disease.

Studies have demonstrated safety and immune response to the quadrivalent HPV vaccine in children with HIV, adolescents, and adult men and women; however, long-term efficacy in patients with HIV has not yet been established [Levin et al. 2010; Zurek Munk-Madsen et al. 2017]. It is assumed that the 9-valent HPV vaccine also will elicit an immune response. Studies are currently underway to provide more extensive data on the efficacy of the 9-valent vaccine in the prevention of HPV disease in individuals with HIV.

In the general population, a two-dose vaccine regimen is recommended for individuals younger than 15 years, and the three-dose vaccine regimen is recommended for individuals aged 15 years and older. Recent studies conducted in individuals without HIV suggest that a single- or two-dose regimen may confer equal protection against HPV types 16 and 18 compared with a 3-dose regimen [Kreimer et al. 2015]. For youth aged 9 to 26 years with HIV, the three-dose regimen remains the recommended approach [Meites et al. 2016]. The 9-valent HPV vaccine should be administered according to the CDC standard schedule for immunocompromised adults and children and adolescents (a three-dose regimen over a 6-month period at 0, 2, and 6 months) [Kojic et al. 2014] and should be offered regardless of CD4 cell count. HPV vaccination has been demonstrated to provide high levels of neutralizing antibody for at least 5 years and to be protective in individuals aged 26 years or younger, regardless of history of sexual activity, but the full length of its protection has not been established. Studies are underway to establish the long-term immunogenicity of the 9-valent HPV vaccine [FDA 2017].

The Advisory Committee on Immunization Practices (ACIP) recommends either the 9-valent or quadrivalent HPV vaccine (the bivalent and quadrivalent vaccines are no longer distributed in the United States) for females and males aged 9 to 26 years with HIV regardless of prior Pap results [McKenzie et al. 2010]. In individuals who have had an abnormal Pap test before being vaccinated, the HPV vaccine may protect against infection from HPV types other than those that caused earlier or existing abnormalities. See *AIDSinfo* > *Human Papillomavirus Disease* for more information about HPV vaccination in populations with HIV [Steinbrook 2006].

HPV testing is not recommended before vaccine administration. It is unlikely that an individual will have been infected with all HPV types covered by the 9-valent vaccine. It is expected that the 9-valent vaccine will be effective against the types to which the patient has not been exposed. ACIP does not recommend for or against routine revaccination with the 9-valent vaccine in individuals who completed a three-dose series of another vaccine. Clinicians should consider the benefit of protection for individual patients against the additional 5 oncogenic types targeted in the 9-valent vaccine [CDC 2016]. Clinicians should continue to follow recommendations for cervical and anal screening, and visual inspection of the anogenital area during annual examinations in all patients with HIV, regardless of the patient's HPV vaccination status. For additional information, see the NYSDOH AIDS Institute guidelines *Cervical Screening for Dysplasia and Cancer* and *Anal Dysplasia and Cancer*.

KEY POINTS

- The 9-valent HPV vaccine is the current formulation for immunization in people with HIV.
- HPV vaccination may be given at the same time as the standard adolescent vaccines offered at age 11 to 12 years. For young people who have experienced sexual abuse or assault or are immune compromised, the vaccine series should begin at age 9 years. HPV testing before administration of the HPV vaccine is not recommended.
- Although HPV vaccination is highly effective in preventing HPV-related warts, dysplasia, and cancer, it does not protect against all HPV types, and it may not fully protect every person who is vaccinated; therefore, clinicians should continue to perform full anogenital evaluations at the recommended intervals for all individuals with HIV who have received the HPV vaccine (see the *Screening* section of this guideline for more information).

Condom Use

HPV and other STIs are transmitted primarily through close physical contact involving anogenital or oral mucosal surfaces. Patients should be informed about the risk of acquiring or transmitting HPV infection at all sites of possible exposure. Education about the utility of male (insertive) and female (receptive) condom use should also be provided. Some individuals use female condoms for anal sex [AIDSmap 2018]. Consistent and proper use of latex male condoms may reduce the risk of oncogenic HPV acquisition among women by 70% and may reduce the odds of HPV infection of the penis in heterosexual men by 50%. Penile condoms also may reduce the risk of genital warts by approximately 60% among men and women [Manhart and Koutsky 2002; Winer et al. 2006; Nielson et al. 2010]. Clinicians should also inform patients that HPV infection may be transmitted at areas that are not covered by a condom, such as the scrotum, vulva, or perianal region [Ward and Ronn 2010]. Dental dams will also only protect areas that are covered. In patients with HIV, untreated STIs are associated with an increase in HIV shedding [Johnson and Lewis 2008; Ward and Ronn 2010] and have been associated with an increased risk of transmitting HIV to partners [Fleming and Wasserheit 1999].

Limiting the number of sex partners may reduce the risk of acquiring HPV [Winer et al. 2003]; however, it is often not possible to determine whether a partner is currently infected with HPV because most people with HPV infection are asymptomatic and may not have visible lesions [Koutsky 1997].

KEY POINT

- Consistent and correct condom use is the most effective means of preventing transmission and acquisition of HIV and other STIs.

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Screening

Medical Care Criteria Committee, July 2018

✓ RECOMMENDATIONS

Screening

- Clinicians should continue to perform cervical and anal Pap smears as recommended for individuals with HIV, regardless of their HPV vaccination status (see the NYSDOH AI guidelines *Cervical Screening for Dysplasia and Cancer* and *Anal Dysplasia and Cancer*). (A2)
- Clinicians should examine the neovagina in transgender women who have undergone vaginoplasty to assess for visible HPV lesions at baseline and during the annual comprehensive physical examination. Examination can be done using an anoscope, a small vaginal speculum, or a nasal speculum. (A3)
- Clinicians should ask all patients about sexual behaviors and new sex partners at each routine monitoring visit to assess for risk behaviors that require repeat or ongoing screening. (A3)

HPV testing with cytologic screening enhances the identification of HPV-related cervical disease in individuals with HIV (see the NYSDOH AI guideline *Cervical Screening for Dysplasia and Cancer*). Clinicians should perform cervical and anal cytologic (i.e., Pap) screening for people with HIV according to the recommended guidelines for this population (see the NYSDOH AI guidelines *Cervical Screening for Dysplasia and Cancer* and *Anal Dysplasia and Cancer*). Examination of the anogenital area of patients with HIV to assess for visible HPV lesions is necessary because HPV can also infect the urethra and the external genitalia [Weyers et al. 2010; Tyerman and Abouafia 2012; Leeds and Fang 2016; CDC 2017b; Ehrenpreis and Smith 2017]. Speculum examination of the vagina (includes neovagina) and cervix and anoscopic examination of the anus and lower rectum also may reveal lesions. There are currently no data on urethral screening and treatment, but referral to a urologist will facilitate appropriate assessment and management when this is a concern. Asking patients to provide details about all gender-reassignment and gynecologic surgical procedures they have undergone is essential to determine the type of screening needed.

Recent data demonstrate increased risk of anal dysplasia and rising rates of anal cancer among females with HIV [Gaisa et al. 2017]. 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 for all females with HIV [Kojic et al. 2011; Hessol et al. 2013; Stier et al. 2015; Gaisa et al. 2017] 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 continue at the recommended intervals (see the AI guideline *Anal Dysplasia and Cancer*), regardless of Pap test results. Although there are no specific data on transgender men or women, the recommendation is extended to also perform anal screening for these populations.

➔ KEY POINTS

- Assessment for visible HPV lesions in individuals with HIV can be accomplished through baseline and then annual examination of the peri-urethral and anogenital areas and the vagina and cervix.
- Individuals who have received HPV vaccination should still be screened for cervical and anal disease according to the recommended schedules (for more information, see the AI guidelines *Cervical Screening for Dysplasia and Cancer* and *Anal Dysplasia and Cancer*).

Obtaining a Sexual History

When obtaining a sexual history, questions should focus primarily on the patient's sexual behavior and not solely on sexual and gender identity (e.g., avoid use of such labels as "lesbian," "homosexual," or "gay") [Lanier et al. 2014]. A study conducted in New York City found that self-reported sexual identity could not independently establish patients' risk. Many men who have sex with men in the study did not identify as "gay," underscoring

the importance of assessing sexual behavior when determining a patient's risk [Pathela et al. 2006; Bernstein et al. 2008]. Transgender people differ widely in terms of sexual behavior and anatomy. It is helpful to ask about the type of sex a person is having and the parts of anatomy used for sex, as well as about the anatomy of partners. A patient's openness to discuss his or her sexual and gender identity may be important for the clinician's understanding of the patients' health status, perceived stigma, and risk of acquiring or transmitting sexually transmitted infections (STIs) [Lanier et al. 2014; CDC 2017a]. Therefore, clinicians should stress the confidential nature of discussions about sexual activities and maintain a nonjudgmental attitude to encourage patients to disclose all sexual behaviors.

For clinicians who are uncomfortable discussing sexual behaviors and STI transmission risk, training may help increase their comfort level and assist them in developing a nonjudgmental approach to educating patients about the importance of STI screening. The New York State (NYS) Department of Health Clinical Education Initiative Line (866-637-2342) enables clinicians in NYS to discuss post-exposure prophylaxis, pre-exposure prophylaxis, HIV, hepatitis C virus, and STI management with a specialist, and the New York City STD/HIV Prevention Training Center provides HIV-related educational resources and training for providers. The Centers for Disease Control and Prevention's *Guide to Taking a Sexual History* offers parameters for discussing sexual health issues with patients.

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Presentation and Diagnosis

Medical Care Criteria Committee, July 2018

✓ RECOMMENDATIONS

Presentation and Diagnosis

- Clinicians with limited expertise should refer individuals with abnormal anogenital physical findings, such as warts, hypopigmented or hyperpigmented plaques/lesions, lesions that bleed, or any other lesions of uncertain etiology for expert evaluation. This evaluation may include colposcopy, high-resolution anoscopy, and/or biopsy. (A3)
- Clinicians should maintain a low threshold for obtaining biopsies of lesions that are atypical in appearance, condylomatous, that are hyper- or hypopigmented or variegated, or that fail to respond to standard treatment. (A3)
- Clinicians should refer for or perform colposcopy for individuals with HIV who have abnormal cervical cytology (including persistent atypical squamous cells of undetermined significance) and high-risk human papillomavirus (HPV) (see the NYSDOH AI guideline *Cervical Screening for Dysplasia and Cancer*). (A2)
- Clinicians should refer for or perform high-resolution anoscopy for individuals with HIV who have abnormal anal cytology, who have visible anal lesions, or if palpable lesions are elicited on digital anorectal examination. (A2)
- Clinicians should refer individuals with visible urethral lesions to a urologist experienced in HPV biopsy and diagnosis. (A3)
- Clinicians should diagnose, treat, and follow-up HPV-related lesions in patients with HIV in consultation with a clinician experienced in the management of HPV and HIV. (A3)

Diagnosis of external condylomata acuminata is often made on the basis of clinical appearance. The appearance of warts varies. Condylomata acuminata (genital warts) can be smooth and skin-colored or hyperpigmented papules or plaques that may be flat, hyperkeratotic, nodular, or exophytic. Symptoms may be absent or may include itching, bleeding, burning, and discomfort. Warts on the external genitalia and the cervix are commonly flat, plaque-like lesions. They also can be exophytic and visible to the naked eye. Cervical lesions are best visualized by colposcopy. Penile lesions can occur along the shaft, but also may be along the penile urethra and hidden from view.

Small external lesions often are treated without biopsy. Lesions that are atypical or variegated in color or shape require biopsy to exclude squamous intraepithelial lesions (SIL) or cancer. Clinicians should maintain a low threshold to obtain biopsy of the following: atypical-appearing lesions; pigmented, internal, or condylomatous lesions; rapidly growing lesions; or lesions that fail to respond to standard treatment, because these may be indicative of precancerous or cancerous lesions.

Manifestations of HPV infection in the setting of HIV infection [Palefsky et al. 1998, 2001a, 2001b; Frisch et al. 2000; Lillo et al. 2001; Minkoff et al. 2001]:

- Condylomata acuminata, anal SIL/anal intraepithelial neoplasia, and cervical SIL/cervical intraepithelial neoplasia have all been reported to occur more frequently in people with HIV.
- With increased immunosuppression, there is evidence for increased risk of the following:
 - Persistent and recurrent HPV infection and disease of the anal and genital tracts.
 - Decreased rates of spontaneous disease regression.
 - Increased severity of HPV disease.
 - Anal SIL.
 - Cervical SIL.
 - Development of condylomata acuminata.
- HPV may be more difficult to treat and more likely to recur with advanced immunosuppression.
- Patients with more advanced immunosuppression have an increased relative risk of developing HPV-related invasive anogenital cancers.

- See the following sources for images:
 - U.S. Department of Veterans Affairs Image Library > Human Papillomavirus Virus
 - CDC Public Health Image Library > Quick Search > HPV
 - Medscape: Diagnosis and Management of Genital Warts in HIV Disease
 - MedicineNet.com > Sexually Transmitted Diseases

Data are mixed regarding the contribution of HIV-related immune suppression to the relapse and progression of HPV disease, and whether antiretroviral therapy (ART)-mediated immune reconstitution can lead to regression of SIL associated with HPV infection [Adler 2010; Blitz et al. 2013; Piketty et al. 2013]. Although there are cases of involution of mucocutaneous warts after initiation of ART, the prevalence or course of anogenital HPV disease is not altered significantly by ART [Adler 2010; Lofgren et al. 2015].

KEY POINTS

- Cervical and anogenital symptoms of HPV-associated disease include itching, bleeding, pain, or spotting after sexual intercourse. HPV-associated disease should be considered in the differential diagnosis when symptoms are present.
- Failure to correctly diagnosis precancerous or cancerous HPV-related disease in a timely manner can cause delay of appropriate therapy and possible mortality. Therefore, clinicians should maintain a low threshold for obtaining biopsies of lesions that are atypical in appearance, condylomatous, have variegated pigmentation, or that fail to respond to standard treatment.

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Treatment

Medical Care Criteria Committee, July 2018

✓ RECOMMENDATIONS

Treatment

- Clinicians should use the same therapeutic modalities in patients with and without HIV when treating HPV, with the exception of sinecatechin use; sinecatechins should not be used in immune-compromised individuals. (A3)
- Clinicians should obtain a biopsy to exclude dysplasia or cancer for condyloma that have not responded to treatment. (A3)
- Clinicians should switch treatment modalities if biopsy-confirmed warts/condyloma have not improved substantially within 4 months of therapy. (A3)
- Clinicians should refer patients with lesions that are resistant to topical therapies; that change in appearance; that have ulceration, irregular shape, or variegated pigmentation; or with biopsy-proven dysplasia to clinicians experienced in the management of HPV and HIV. (A3)
- Clinicians should refer patients with visible urethral lesions to a urologist for treatment. (A3)
- Clinicians should refer patients with HIV who have anogenital cancer to an oncologist for treatment. (A3)
- Clinicians should avoid imiquimod during pregnancy unless the benefits outweigh the risk. (A3)
- Clinicians should not use sinecatechins, podophyllin, or podofilox (podophyllotoxin) in pregnant individuals. (A3)
 - See the Centers for Disease Control and Prevention's [CDC] guideline on *Anogenital Warts*.

The standard therapeutic approach to treating HPV-related nonmalignant lesions (condyloma/warts) and dysplasia (squamous intraepithelial lesion or above) in individuals with HIV is the same as that for individuals without HIV. Treatment of condyloma is aimed at removing symptomatic visible warts. However, some untreated warts may resolve spontaneously. To date, there has been no evidence that any available treatment regimen eradicates infection. Comparative efficacy trials of the different treatment options for patients with HIV have not been conducted. Treatment of precancerous lesions includes ablation using cryotherapy or laser, and surgical or laser excision. These procedures should be performed only by experienced clinicians (see the AIDS Institute guideline *Cervical Screening for Dysplasia and Cancer* for more information).

Cryotherapy, electrocautery, podophyllotoxin, interferon, imiquimod, cidofovir gel, trichloroacetic acid, and bichloroacetic acid have all demonstrated efficacy treating anogenital warts in patients without HIV. In a systematic review and meta-analysis, electrocautery and imiquimod were shown to be efficacious in the treatment of anogenital warts in people with HIV [Werner et al. 2017]. Controlled studies of other HPV interventions in people with HIV have not been done. Interferon, 5-fluorouracil, and podophyllotoxin are no longer preferred HPV treatments in the primary care setting because of low efficacy and toxicity that may limit their routine use [Lacey et al. 2013]. The safety and efficacy of sinecatechins has not been evaluated in individuals with HIV and therefore should not be used [FDA 2007].

There are limited data on imiquimod use in pregnancy, but animal data suggest low risk of harm. This drug can be used during pregnancy if no other options, including waiting until after delivery, are available. Due to a lack of safety data, podophyllin should not be used during pregnancy. Podofilox (podophyllotoxin) is contraindicated in pregnancy [Briggs et al. 2017].

Data for the treatment of HPV lesions of the neovagina, whether penile or colonic in origin, are limited to case reports and small case series. Standard, provider-applied approaches to treatment should be used [Fiumara and Di Mattia 1973; Liguori et al. 2004; Wasef et al. 2005; Matsuki et al. 2015; van der Sluis et al. 2016; Labanca and Manero 2017].

Clinicians often report poor clearance rates after therapy in patients with HIV [Richel et al. 2013]. More than one application of therapy, more than one method of treatment (e.g., topical imiquimod followed by cryotherapy), or longer duration of treatment is often needed. Treatment length may vary and frequent visits (as often as biweekly) are necessary to assess lesion regression and side effects. Topical treatments may cause side effects such as irritation and a burning sensation, which may affect treatment adherence. The response to treatment and its side

effects should be evaluated throughout the course of therapy. The treatment approach may need to be changed if a patient has not improved substantially after standard therapy. There are no data available regarding effects of HPV treatment on HPV transmissibility.

Clinical judgment should inform a clinician's decisions about whether to treat a patient with HIV for anogenital warts or refer the patient to a specialist. The following factors should be considered when making this decision: clinician experience and available resources, diagnostic certainty, anatomic site of lesions, potential adverse effects of treatment, and patient ability to adhere to treatment.

Table 1, below, lists available treatment options for condyloma for patients with HIV.

Table 1: Available Treatment Options for Anogenital Condyloma for Patients with HIV (adapted from CDC 2015, unless otherwise noted)		
Condyloma Type	Treatment	Comments
Anogenital Condyloma	<ul style="list-style-type: none"> ▪ Cryotherapy ▪ Podophyllin resin 10%–25% in a compound tincture of benzoin* ▪ Surgical excision ▪ Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90%* <p>Patient self-administered treatments:</p> <ul style="list-style-type: none"> ▪ Imiquimod 3.75% or 5% cream (may decrease likelihood of recurrences) ▪ Podofilox 0.5% solution or gel* 	<ul style="list-style-type: none"> ▪ Extra-genital warts, including warts on penis, groin, scrotum, vulva, perineum, external anus, and peri-anus ▪ Weakens condoms and vaginal diaphragms
Urethral Meatus Condyloma	<ul style="list-style-type: none"> ▪ Cryotherapy with liquid nitrogen ▪ Surgical excision 	—
Vaginal Condyloma	<ul style="list-style-type: none"> ▪ Cryotherapy with liquid nitrogen ▪ Surgical excision 	—
Cervical Condyloma	<ul style="list-style-type: none"> ▪ Cryotherapy with liquid nitrogen ▪ Surgical excision ▪ TCA or BCA 80%–90% solution 	<ul style="list-style-type: none"> ▪ Management of cervical warts should include consultation with a specialist ▪ For those who have exophytic cervical warts, a biopsy evaluation to exclude high-grade squamous intraepithelial lesions must be performed before treatment is initiated
Neovaginal Condyloma [Fiumara and Di Mattia 1973; Liguori et al. 2004; Wasef et al. 2005; Matsuki et al. 2015; van der Sluis et al. 2016; Labanca and Manero 2017]	<ul style="list-style-type: none"> ▪ Cryotherapy ▪ Imiquimod 3.75% or 5% cream (may decrease likelihood of recurrences) ▪ Podofilox 0.5% solution or gel* ▪ Podophyllin resin 10%–25% in a compound tincture of benzoin* ▪ Surgical excision ▪ TCA or BCA 80%–90%* 	<ul style="list-style-type: none"> ▪ Weakens condoms and vaginal diaphragms
<p>*Imiquimod, podophyllin, and podofilox (podophyllotoxin), and sinecatechins should not be used in pregnant individuals [Briggs et al. 2017]. TCA or BCA can be used to treat small external warts during pregnancy but may not be as effective. Sinecatechins should not be used in any individual with HIV because safety and efficacy data do not exist [FDA 2007].</p>		

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Partner Exposure to HIV and HPV

Medical Care Criteria Committee, July 2018

✓ NYS REQUIREMENTS AND CLINICAL RECOMMENDATIONS

Partner Exposure to HIV and HPV

- NYS Public Health Law requires that medical providers talk with individuals with HIV about their options for informing their sex partners that they may have been exposed to HIV, including the free, confidential partner notification assistance offered by New York State Department of Health (NYSDOH) and New York City Department of Health and Mental Hygiene.
- When a patient with HIV is diagnosed with human papillomavirus (HPV), clinicians should advise the patient to encourage sex partners to seek evaluation for possible exposure to both HPV and HIV. (A3)

Treatment of lesions solely for the prevention of future transmission cannot be recommended because the value of treatment in reducing infectivity is not known. However, sex partners of patients who have genital lesions might benefit from counseling and examination to assess the presence of genital warts and HPV-related dysplasia. Sex partners should also be evaluated for the presence of other sexually transmitted infections (STIs), including HIV, because HPV disease is transmitted sexually [Workowski and Bolan 2015].

Clinicians should inform patients that any sex partner who does not have confirmed HIV infection should have routine HIV testing for early identification of HIV acquisition. If a patient with an HIV exposure presents within 36 hours, evaluation for non-occupational post-exposure prophylaxis (PEP) should occur. When possible, onsite availability of HIV testing and STI treatment for partners is ideal because it may increase the likelihood that partners will receive timely access to HIV testing and appropriate treatment, including HIV post-exposure prophylaxis and treatment for the STI as needed (see NYSDOH AIDS Institute [AI] guideline *PEP for Non-Occupational Exposure to HIV*). Such strategies may also increase identification of individuals who require ongoing medical care. Partner education about reducing high-risk behaviors, including counseling about the use of barriers, such as male/insertive and female/receptive condoms, and making condoms visibly available in the clinic, may further decrease the risk of transmission of both HIV and other STIs. Patients who remain at high risk of exposure after completing a course of nPEP and who are negative for HIV at the time of the 4-week test should be offered pre-exposure prophylaxis (PrEP), to begin immediately after the last dose of nPEP (see NYSDOH AI guideline *PrEP to Prevent HIV and Promote Sexual Health*). Patient education about Undetectable=Untransmittable (U=U) as an HIV prevention strategy should stress that an undetectable HIV viral load prevents only the sexual transmission of HIV. Consistent and correct condom use remains the best method for preventing pregnancy and the transmission of STIs other than HIV.

The NYSDOH Partner Services program provides assistance to individuals with HIV and to care providers who would like help notifying a patient's sex partner(s) of possible exposure to HIV, chlamydia, gonorrhea, or syphilis. Available options for partner notification include anonymous notification from the local health department, dual disclosure (patient disclosure with the help of Partner Services staff), and self-disclosure. Partner Services staff within local health departments work with patients to develop a plan to notify their partners, whether that plan includes staff notifying potentially exposed partners anonymously or helping patients who choose to tell their partners on their own develop a notification plan and strategy.

KEY POINTS

- When a patient with HIV is diagnosed with a new STI, the clinician should inform the patient about the implications of the diagnosis for his/her sex partner(s):
 - A new STI diagnosis signals that the patient was engaging in sexual behaviors that place sex partners at increased risk of acquiring HIV infection.
 - The local health department may contact a sex partner confidentially about the potential exposure and treatment options.
- Clinicians should provide patients with information and counseling about notifying partners, risk reduction, and safer sex practices.

Reference

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All Recommendations

Sexually Transmitted Infections Guidelines Committee, February 2018

✓ ALL RECOMMENDATIONS

Transmission and Prevention

- Clinicians should recommend the 9-valent human papillomavirus (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, prior cervical or anal Pap test results, HPV-related cytologic changes, or history of HPV lesions. (A3)
- Clinicians should inform patients with HIV about the risk of acquiring HPV and other sexually transmitted infections (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. (A3)

Screening

- Clinicians should continue to perform cervical and anal Pap smears as recommended for individuals with HIV, regardless of their HPV vaccination status (see the NYSDOH AI guidelines *Cervical Screening for Dysplasia and Cancer* and *Anal Screening for Dysplasia and Cancer*). (A2)
- Clinicians should examine the neovagina in transgender women who have undergone vaginoplasty to assess for visible HPV lesions at baseline and during the annual comprehensive physical examination. Examination can be done using an anoscope, a small vaginal speculum, or a nasal speculum. (A3)
- Clinicians should ask all patients about sexual behaviors and new sex partners at each routine monitoring visit to assess for risk behaviors that require repeat or ongoing screening. (A3)

Presentation and Diagnosis

- Clinicians with limited expertise should refer individuals with abnormal anogenital physical findings, such as warts, hypopigmented or hyperpigmented plaques/lesions, lesions that bleed, or any other lesions of uncertain etiology for expert evaluation. This evaluation may include colposcopy, high-resolution anoscopy, and/or biopsy. (A3)
- Clinicians should maintain a low threshold for obtaining biopsies of lesions that are atypical in appearance, condylomatous, that are hyper- or hypopigmented or variegated, or that fail to respond to standard treatment. (A3)
- Clinicians should refer for or perform colposcopy for individuals with HIV who have abnormal cervical cytology (including persistent atypical squamous cells of undetermined significance) and high-risk human papillomavirus (HPV) (see the NYSDOH AI guideline *Cervical Screening for Dysplasia and Cancer*). (A2)
- Clinicians should refer for or perform high-resolution anoscopy for individuals with HIV who have abnormal anal cytology, who have visible anal lesions, or if palpable lesions are elicited on digital anorectal examination. (A2)
- Clinicians should refer individuals with visible urethral lesions to a urologist experienced in HPV biopsy and diagnosis. (A3)
- Clinicians should diagnose, treat, and follow-up HPV-related lesions in patients with HIV in consultation with a clinician experienced in the management of HPV and HIV. (A3)

Treatment

- Clinicians should use the same therapeutic modalities in patients with and without HIV when treating HPV, with the exception of sinecatechin use; sinecatechins should not be used in immune-compromised individuals. (A3)
- Clinicians should obtain a biopsy to exclude dysplasia or cancer for condyloma that have not responded to treatment. (A3)
- Clinicians should switch treatment modalities if biopsy-confirmed warts/condyloma have not improved substantially within 4 months of therapy. (A3)
- Clinicians should refer patients with lesions that are resistant to topical therapies; that change in appearance; that have ulceration, irregular shape, or variegated pigmentation; or with biopsy-proven dysplasia to clinicians experienced in the management of HPV and HIV. (A3)

Continued next page

✓ ALL RECOMMENDATIONS – CONTINUED**Treatment, *continued***

- Clinicians should refer patients with visible urethral lesions to a urologist for treatment. (A3)
- Clinicians should refer patients with HIV who have anogenital cancer to an oncologist for treatment. (A3)
- Clinicians should avoid imiquimod during pregnancy unless the benefits outweigh the risk. (A3)
- Clinicians should not use sinecatechins, podophyllin, or podofilox (podophyllotoxin) in pregnant individuals. (A3)
 - See the Centers for Disease Control and Prevention’s [CDC] guideline on *Anogenital Warts*.

Partner Exposure to HIV and HPV

- NYS Public Health Law requires that medical providers talk with individuals with HIV about their options for informing their sex partners that they may have been exposed to HIV, including the free, confidential partner notification assistance offered by New York State Department of Health (NYSDOH) and New York City Department of Health and Mental Hygiene.
- When a patient with HIV is diagnosed with human papillomavirus (HPV), clinicians should advise the patient to encourage sex partners to seek evaluation for possible exposure to both HPV and HIV. (A3)

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How This Guideline Was Developed

July 2018

The New York State (NYS) 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 (MCCC) 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 care to individuals with HIV. The purpose of the *Human Papillomavirus in Patients with HIV* clinical practice guideline is to inform primary care providers and other practitioners in NYS about HPV-related cervical and anal disease and to identify opportunities for screening and treatment.

Committee Makeup: Members of the MCCC (see Box A1: *MCCC Leaders and Members and HPV Guideline External 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 AI Office of the Medical Director (see *Funding and 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 A1)

- **Chair Emeritus:** Samuel T. Merrick, MD (*as of March 15, 2018; formerly Chair*)
- **Chair:** Joseph P. McGowan, MD, FACP, FIDSA (*as of March 15, 2018; formerly Vice-Chair*)
- **Vice-Chair:** Steve Fine MD, PhD (*as of March 15, 2018; formerly Contributing Member*)
- **Chair Emeritus:** Judith A. Aberg, MD, FIDSA, FACP (*stepped down on March 15, 2018*)
- Gina M. Brown, MD
- Charles J. Gonzalez, MD, AI Medical Director (*as of May 2018; formerly Associate Medical Director for Science and Policy*)
- Asa Radix, MD, MPH, FACP (*joined committee in March 2018*)
- **JHU Principal Investigator:** Christopher J. Hoffmann, MD, MPH

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 HPV Guideline External Reviewers

Leadership

- **Chair:** Samuel T. Merrick, MD (*Chair Emeritus, effective March 2018*)
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- **Vice-Chair:** Steven M. Fine, MD, PhD, University of Rochester Medical Center, Rochester, NY (*effective March 2018*)
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Funding and Disclosure of Potential Conflicts of Interest (COIs)

Funding: NYS funds supported development of the *HPV in Patients with HIV* guideline through a grant awarded to the JHU School of Medicine, Division of Infectious Diseases, from the NYSDOH AI.

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 nonexistent.

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	
Committee Member’s Role	Relationships disclosed for the previous and/or upcoming 12 months
Planning Group Member	Research support: Gilead, ViiV Healthcare; scientific advisor: Merck
Planning Group Member	Scientific advisor: Merck
Committee Member	Scientific advisor: GFORCE
Committee Member	Consultant: Roche Diagnostics
Committee Member	Consultant: Gilead, Merck, ViiV, BMS
Expert Consultant	Research support: Antiva, Ubiome, Agenovir Scientific advisor: Merck, Ubiome, Antiva, Agenovir
Expert Consultant	Research support: Glaxo Smith Kline/ViiV Healthcare, Bristol Myers–Squibb, Gilead; honorarium recipient: Glaxo Smith Kline/ViiV Healthcare; shareholder (spouse): Johnson & Johnson

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.

→ Box A3: Evidence Collection and Review Processes

- NYSDOH AI and MCCC defined the goal of the guideline: To provide evidence-based clinical recommendations for the prevention and management of HPV-related cervical and anal disease.
- 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
- Lead author reviewed studies identified through searches, and excluded based on the following criteria:
 - Based on publication type, study design, participants and clinical relevance to the guideline.
- Author and editorial staff conducted additional searches using PubMed and online databases to identify:
 - Studies published prior to the 5-year search limit
 - Studies published during the guideline development process
 - Recent conference abstracts
 - Older studies known to provide strong evidence in support of specific recommendations or to undergird expert opinion
 - New York State epidemiologic data
- Lead author developed and all MCCC members reviewed and approved evidence-based guideline recommendations:
 - Planning group reviewed, deliberated, refined, and approved draft recommendations
 - MCCC members reviewed, provided written comment on, deliberated, and reached consensus on recommendations
 - 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
 - Additional evidence identified and cited during the rating process (see below)
- Ongoing update process
 - 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
 - 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
 - JHU editorial staff will track, summarize, and publish ongoing changes to the guideline
 - MCCC reviews and approves substantive changes to, additions to, or deletions of recommendations
 - The Committee will initiate a full review of the guideline 4 years after the original publication date
- NYSDOH AI will publish a comprehensive update 5 years after the original publication date

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 HPV screening and treatment 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 HPV-related cervical and anal disease 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.