

Cervical Cancer Screening Among Women Who Attend Sexually Transmitted Diseases (STD) Clinics: Background Paper for 2010 STD Treatment Guidelines

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Background. In April 2008, experts reviewed updates on sexually transmitted disease (STD) prevention and treatment in preparation for the revision of the Centers for Disease Control and Prevention (CDC) STD Treatment Guidelines. This included a review of cervical cancer screening in the STD clinical setting.

Methods. Key questions were identified with assistance from an expert panel. Reviews of the literature were conducted using the PubMed computerized database and shared with the panel. Updated information was incorporated in the 2010 CDC STD Treatment Guidelines.

Results. We recommend that STD clinics offering cervical screening services screen and treat women according to guidelines by the American College of Obstetrics and Gynecology, the American Cancer Society, the US Preventive Services Task Force, and the American Society for Colposcopists and Cervical Pathologists. New to the 2010 guidelines are higher age for initiating cervical screening (age ≥ 21 years) and less frequent intervals of screening (at least every 3 years). New recommendations include new technologies, such as liquid-based cytology and high-risk human papillomavirus (HPV) DNA tests. Liquid-based technologies are not recommended over conventional testing. HPV DNA tests are recommended as adjunct tests and with new indications for use in cervical screening and management. Stronger recommendations were issued for STD clinics offering cervical screening services to have protocols in place for follow-up of test results and referral (eg, colposcopy).

Conclusions. Important additions to the 2010 STD Treatment Guidelines include information on updated algorithms for screening and management of women and recommendations for use of liquid-based cytology and high-risk HPV testing.

In April 2008, experts on sexually transmitted diseases (STDs) were convened to review updates on STD prevention and treatment in preparation for the 2010 revision of the Centers for Disease Control and Prevention (CDC) STD Treatment Guidelines. At this meeting, there was a discussion of important updates on cervical cancer screening in the STD clinical setting, including new human papillomavirus (HPV) testing technology, appropriate intervals and ages for screening, management and referral of women with abnormal screening test

results, and screening in special populations (eg, pregnant women and HIV-infected women). Key questions on cervical screening were generated before the meeting. Comprehensive literature reviews were conducted, and all relevant publications and findings were then reviewed in consultation with these experts. These consultations resulted in drafting of the new chapter on cervical screening in the STD clinic setting.

METHODS

The key questions generated by the expert panel are listed here for completeness; all are discussed in this article, except for the final question (regarding counseling messages), which is discussed in another article in this issue:

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- Should STD clinics have cervical cancer screening programs?
- What ages of women should be screened in the STD setting? (include considerations for liquid-based vs conventional Pap testing)
- If cervical screening is performed, is there a preferential order for specimen collection?
- What are the management options for abnormal screening test results?
- What are the considerations for follow-up and referral services for positive screening test results?
- What is the role of high-risk (HR) HPV DNA testing in cervical screening programs? How should it be used in the STD clinic setting?
- When should HR HPV DNA testing expressly not be performed?
- What are special considerations for
 - pregnant women,
 - HIV-infected women (especially with respect to HPV testing),
 - women with history of cervical intraepithelial neoplasia (CIN) or treatment on the cervix (cryotherapy, loop electro-surgical excision procedure, or cone biopsy), and
 - women who have had hysterectomy?
- What counseling messages should be given to women about
 - purpose of Pap screening,
 - meaning of normal Pap test and positive HPV test results,
 - meaning of atypical squamous cells of undetermined significance (ASC-US) test result,
 - disclosure to sex partners about an abnormal Pap or positive HR HPV test result, and
 - prevention measures for current and future sex partners and risk reduction for the patient?

The key questions guided a systematic review of scientific literature. Our literature review process involved a search of English-language literature using the PubMed computerized database of the US National Library of Medicine during the period 2006–2010. We used the following Medical Subject Heading (MeSH) search terms: papillomavirus infections, papillomavirus vaccines, Papanicolaou test, Papanicolaou smear, sexually transmitted disease, diagnosis, pregnancy, guidelines (publication type), practice guideline (publication type). The following free text search terms were also used: HPV, human papillomaviruses, sexually transmitted disease clinics, HPV DNA tests, cervical cancer screening guidelines or recommendations, Pap testing guidelines or recommendations, Pap specimen adequacy, primary screening test, cervical specimen collection order, pregnancy, cervical screening, HIV infection, HIV infected persons, HPV test triage, and HPV test primary screen. Results of these searches were then further limited to

those that also included the free text terms “cervical screening” or “Pap screening.” These publications were then reviewed for relevance and used if appropriate. We also searched abstracts from major STD- and HIV-related meetings during the past 5 years with the same terms using conference Web sites. We considered their data if the abstracts had not yet resulted in published articles.

We also reviewed relevant publications and policy statements from major organizations, including US Preventive Services Task Force (USPSTF), American Cancer Society (ACS), American College of Obstetrics and Gynecology (ACOG), American Society for Colposcopy and Cervical Pathology (ASCCP), National Institutes of Health, Infectious Diseases Society of America (IDSA), and the CDC.

Most publications identified through literature review covered the topic of cervical cancer screening not specific to any clinical settings, such as STD clinics (with the exception of a handful of articles mentioned as such and articles regarding HIV-care clinical settings). Therefore, we did not limit our evidence to publications about the STD clinical setting. Instead, we identified information that would be useful in any clinical setting and could be applied to STD clinic patients.

The relevant articles were summarized and shared with the expert panel. Panel members gave feedback on the summaries and used them to draft the new chapter.

RESULTS

Although there are no published papers reviewing whether cervical screening should be performed in the STD clinical setting, the decision to provide screening is a complex one based upon ability to meet ongoing needs for infrastructure for ongoing staff training and education, laboratory services, and appropriate follow up and management of screened women. There are 3 articles and 1 abstract about frequency of abnormal Pap test results and HPV infection in cervical screening programs specific to STD clinical settings [1–4]. One study, which took place during 2003–2005, of a sentinel network of STD clinics reported 27% prevalence of HR HPV DNA (by Hybrid Capture 2 testing; Qiagen) and 18% prevalence of abnormal Pap tests (ASC-US or worse) among patients aged 14–65 years who were eligible for routine cervical screening [5]. Thirty-two percent of the population aged 14–65 years was at increased risk of cervical cancer due to HPV infection, cervical disease, or history of cervical disease. In 2004, 49% of all STD clinics in the United States reported providing cervical screening services, and 20% reported use of HPV DNA testing [4].

For the newest STD Treatment Guidelines, the CDC will continue to use currently available guidelines (Table 1) to dictate the age range for screening, because clinic populations and resources available may vary. The ACOG recommends that

Table 1. Cervical Cancer Screening Guidelines

	American Cancer Society (ACS) ^{a,b} 2002	US Preventive Services Task Force (USPSTF) ^c 2003	American College of Obstetricians and Gynecologists (ACOG) ^d 2009
When to start screening	Approximately 3 y after onset of vaginal intercourse, but no later than age 21 ^e	Within 3 y of onset of sexual activity or age 21, whichever comes first (<i>A recommendation</i>)	Age 21, regardless of the age of onset of sexual activity. Should be avoided before age 21. (<i>Level A evidence</i>)
Screening method & intervals			
Conventional cytology	Annually; every 2–3 y for women age ≥ 30 y with a history of 3 negative cytology tests. ^f Sexual history should not be used as a rationale for more frequent screening.	At least every 3 y (<i>A recommendation</i>)	Every 2 y from age 21 to 29 y (<i>Level A evidence</i>); every 3 y for women age ≥ 30 y with a history of 3 negative cytology tests. ^f (<i>Level A evidence</i>)
Liquid-based cytology	Every 2 y; every 2–3 y for women age ≥ 30 y with a history of 3 negative cytology tests. ^f Sexual history should not be used as a rationale for more frequent screening.	Insufficient evidence (<i>I recommendation</i>)	Every 2 y from age 21 to 29 y (<i>Level A evidence</i>); every 3 y for women age ≥ 30 y with a history of 3 negative cytology tests. ^f (<i>Level A evidence</i>)
HPV co-test (cytology + HPV test)	Not recommend <30 y. Age ≥ 30 y, no more than every 3 y if HPV negative, cytology normal. Sexual history should not be used as a rationale for more frequent screening.	Insufficient evidence (<i>I recommendation</i>)	Age ≥ 30 y, no more than every 3 y if HPV negative, cytology normal (<i>Level A evidence</i>), even with new sexual partners. Not recommended for women <30 y.
Primary HPV testing ^g	Not FDA approved	Not FDA approved	Not FDA approved
When to stop screening	Women age ≥ 70 y with ≥ 3 recent, consecutive negative tests and no abnormal tests in prior 10 y. ^f At-risk women ^f should continue screening as long as they are in reasonable health.	Women age >65 y with adequate recent screening with normal Pap tests, who are not otherwise at high risk for cervical cancer (<i>D recommendation</i>)	Between age 65–70 y with 3 consecutive normal cytology tests and no abnormal tests in the past 10 y (<i>Level B evidence</i>); an older woman who is sexually active and has multiple partners should continue to have routine screening.
Screening after total hysterectomy	If removal for benign disease and no history of high-grade CIN or worse, may discontinue screening. Women with an undocumented history should be screened until 3 consecutive normal tests and no abnormal tests within a 10-y period are achieved.	Discontinue if removal for benign disease. (<i>D recommendation</i>)	If removal for benign disease and no history of high-grade CIN or worse, may discontinue screening. (<i>Level A evidence</i>) Women for whom a negative history cannot be documented should continue to be screened. (<i>Level B evidence</i>)
Need for a pelvic exam	The ACS and others should educate women, particularly teens and young women, that a pelvic exam does not equate to a cytology test and that women who may not need a cytology test still need regular health care visits including gynecologic care. Women should discuss the need for pelvic exams with their providers.	Not addressed	Physicians should inform their patients that annual gynecologic examinations may be appropriate. (<i>Level C evidence</i>) ^h

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Table 1 continued.

	American Cancer Society (ACS) ^{a,b} 2002	US Preventive Services Task Force (USPSTF) ^c 2003	American College of Obstetricians and Gynecologists (ACOG) ^d 2009
Screening among those immunized against HPV 16/18	It is critical that women, whether vaccinated or not, continue screening according to current ACS early detection guidelines.	Not addressed	Recommendations remain the same regardless of vaccination status. (Level C evidence)

Abbreviations: CIN, cervical intraepithelial neoplasia; DES, Diethylstilbestrol; HIV, human immunodeficiency virus; HPV, human papillomavirus.

^a Saslow D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 2002; 52:342–62.

^b Saslow D, et al. American Cancer Society guideline for HPV vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin* 2007; 57:7–28.

^c USPSTF. Screening for cervical cancer. January 2003. Available at: <http://www.ahrq.gov/clinic/3rduspstf/cervcan/cervcanrr.pdf>.

^d ACOG Practice Bulletin no. 109: Cervical cytology screening. ACOG Committee on Practice Bulletins—Gynecology. *Obstet Gynecol* 2009;114:1409–20.

^e Provider discretion and patient choice should be used to guide initiation of screening in women aged ≥ 21 years who have never had vaginal intercourse and for whom the absence of a history of sexual abuse is certain.

^f Some exceptions apply (eg, women who are immunocompromised or HIV positive, have a history of prenatal exposure to DES, were previously treated for CIN 2 or 3 or cancer).

^g Primary HPV testing is defined as conducting the HPV test as the first screening test. It may be followed by other tests (such as a Pap) for triage.

^h More specific guidance from 2003 states that an annual pelvic examination is a routine part of preventive care for all women age ≥ 21 years even if they do not need cervical cytology screening (Level C evidence).

women start cervical screening with Pap tests at 21 years of age regardless of sexual activity [6]. The ACS and the USPSTF recommend either starting at age ≥ 21 years (ACS) or within 3 years after initiating sexual activity (USPSTF), whichever is earlier. Screening should continue at least every 3 years up to age 65 years (USPSTF) or 70 years (ACS) [7, 8]. ACOG states that screening can be discontinued in women aged 65–70 years [7].

In summary, we recommend that, at STD clinics where cervical screening is being conducted, screening should be initiated at age 21 years or within 3 years after initiating sexual activity. Screening should continue at intervals of at least every 3 years and should be discontinued at age 65–70 years. At the time of this writing, both ACS and USPSTF are revising their guidelines and upon publication, updated guidelines should be utilized.

Although liquid based testing may be desirable due to ease of HPV specimen collection and concomitant testing as well as laboratory choice to conduct liquid based testing, at this time, there are no data to preferentially recommend the newer technology of liquid-based cytologic testing over conventional cytology. Conventional cytology is a comparatively inexpensive, effective, and appropriate test method for cervical screening. A recent meta-analysis of 9 studies comparing the 2 cytologic test types found no improvement in sensitivity or specificity by using liquid-based cytologic testing [9]. A randomized clinical trial reported comparable sensitivity between the 2 test types [10].

STD clinics offering cervical cancer screening are encouraged to use cytopathology laboratories that are Clinical Laboratory Improvement Amendments (CLIA)–certified and report results using the 2001 Bethesda System of classification. HPV DNA testing should be limited to HR HPV testing only. HPV DNA tests should be processed in CLIA–certified labs [11].

There are no data to suggest a preferential order for cervical specimen collection. One recent study showed no impact of

specimen order on liquid-based Pap test adequacy (or adequacy of gonorrhea and chlamydia tests) when separate specimens were collected for cervical cytology, gonorrhea, and chlamydia [12]. Another study showed no influence on test performance of conventional cytologic test or HPV DNA tests based on specimen collection order [13].

The CDC recommends management strategies for cytology test results based on 2006 consensus guidelines published by the ASCCP [14]. The ACOG has recommended management strategies based on ASCCP guidelines [15]. The USPSTF and ACS do not typically provide guidance on management strategies (except for ACS, which recommends HPV DNA testing for triage of women with ASC-US cytology).

Management of women with abnormal screening (cervical cytology) or diagnostic test results (cervical biopsies) is outlined in ASCCP 2006 guidelines and may require periodic HR HPV DNA testing, cytologic testing, and procedures on the cervix. Management of these women may be outside the scope of typical care provided in the STD clinic setting, and women would likely receive better care from providers with more experience in managing these cases.

No new information is available on referral services in the STD clinic setting, but other federally funded programs that provide cervical screening services include Title X and the Breast and Cervical Cancer Early Detection Program.

HPV diagnostic tests that detect viral nucleic acid (ie, DNA or RNA) are available for clinical use in women undergoing cervical cancer screening. These tests should not be used for women < 20 years of age or for STD screening apart from use as indicated in cervical cancer screening. HPV diagnostic tests that detect any of the oncogenic, or HR HPV types, are known as HR HPV tests. There are 3 HR HPV tests that are Food and Drug Administration (FDA) approved: (1) the digene HC2 High-Risk

HPV DNA test (Qiagen), (2) the Cervista High-Risk HPV test (Hologics), and (3) the cobas HPV test (Roche Molecular Diagnostics), which detect the presence of any of 13 (digene) or 14 (Cervista, cobas) HR HPV types. There are 2 FDA-approved tests for type-specific HR HPV testing: the Cervista 16/18 HPV test, which detects and reports type-specific infection with HPV 16 and/or 18, and the cobas HPV test, which in addition to reporting on the presence of any of 14 HPV types, reports specific information about the presence of types 16 and 18. These 2 tests provide information on the actual HPV type(s) present; others report a positive result if any of the types is detected. There is one marketed FDA-approved test, the digene HC2 HPV DNA test (Qiagen), that detects the presence of any of 13 high-risk or 5 low-risk HPV types. There are no clinical indications for this specific test (the digene HC2 HPV DNA test) in the STD clinic setting (or any other clinical setting), because low-risk HPV type testing is not clinically useful. Only HR HPV DNA testing is indicated in certain circumstances. Therefore, the digene HC2 HPV DNA test will not be included in any further discussions of HPV testing in this article.

Test performance characteristics of both assays for HR HPV testing (digene HC2 HR HPV DNA test and Cervista HR HPV test) suggest comparability of sensitivity and specificity, leading to the recommendation by ASCCP that the 2 tests can be used interchangeably. However, a recent analysis suggests that the Cervista HR HPV test may be more sensitive [16]. This finding is most important among women aged ≥ 30 years with normal cytologic test results, because this group is recommended for more frequent follow-up testing according to ASCCP (Table 1). The analysis suggests that more women would test HR HPV positive with the Cervista assay than with the digene assay, resulting in a higher proportion being followed up with more frequent testing. However, because of the different populations sampled using the 2 assays, it is unclear whether Cervista is detecting clinically important infections or merely detecting more false-positive results.

HPV tests can provide very useful information in the context of cervical cancer screening. For example, ASCCP recommends HR HPV testing for triage of women with ASC-US (only for women aged ≥ 21 years) and for cotesting of women aged ≥ 30 years [14].

Because newly acquired HPV infections clear spontaneously and the prevalence of HR HPV DNA positivity decreases with age from a peak in adolescents and women aged 20–29 years, HR HPV testing should not be used for routine screening in women aged < 30 years [14]. HPV tests are not useful and can be misleading when used in other contexts (such as screening men, screening partners, and screening women < 30 years of age). There are data to suggest that providers and laboratorians are not using the HPV tests appropriately. It is for this reason that guidance on proper use of HPV tests and counseling messages for providers and patients are emphasized in the 2010 STD Treatment Guidelines. One report found that 30% of physicians used

the tests inappropriately [17]. A survey of national laboratories found that a substantial proportion offered tests for low-risk HPV testing, an FDA-approved test with no clinical applications [18], HR-HPV DNA testing is not recommended as an STD screening test, as a test for partners, or as a test for men.

Specimens for HR HPV DNA testing can be aliquoted from cervical specimens collected for liquid-based cytology or can be cocollected along with specimens for conventional cytology. Clinical settings (ie, STD clinics) interested in using conventional cytology do not need to adopt liquid-based cytology for the purposes of ease of HPV testing, because cocollection has been demonstrated to be a successful strategy [19].

The Cervista 16/18 HPV test is currently licensed for triage of women aged ≥ 30 years with normal cytology and a positive HR HPV DNA test results. This test provides type-specific information on the presence of HPV 16 and/or 18. The ASCCP has recommended this test as an option for management of this subgroup of women [20]. However, STD programs should consider cost of an additional test to their screening algorithms and long-term outcomes.

HPV DNA testing is not a necessary part of cervical screening programs, however, and may prove to be less useful in high-prevalence populations, such as STD clinic populations. STD clinics can choose whether to offer HPV DNA testing in their clinical settings based on available resources. A study of 8 sentinel STD clinics demonstrated an HR HPV DNA prevalence of 32% among women < 30 years of age (for whom HPV testing is not recommended except in the management of ASC-US) and 14% among women aged ≥ 30 years [4].

Recent studies have examined the usefulness of HPV DNA testing in a primary screening role; however, at present, there is no FDA indication for HPV DNA as a stand-alone primary screening test. Several studies have examined the test performance characteristics of HPV DNA, compared with Pap test, and found higher sensitivity and lower specificity for detection of high-grade cervical lesions [13, 21, 22].

HR HPV DNA testing should not be performed as prevaccination testing, because a positive test result does not identify specific HPV types and women with a positive test result may not have been infected with any vaccine HPV types. HPV 16/18 DNA testing should also not be performed as prevaccination testing, because the women who test positive for these 2 types may still benefit from vaccination against HPV types 6 and 11 if they are receiving the quadrivalent vaccine [23]. Screening for HPV infection with the HPV DNA test should not be performed, because the significance of HPV infection in the absence of clinical disease is of unknown significance. Previous studies have demonstrated a lack of usefulness for HPV DNA testing to triage low-grade squamous intraepithelial lesion (LSIL) cytology because of the high prevalence of HR HPV infection in this group (77% prevalence) [24]. Adolescents aged < 21 years are a population with very

high prevalence of HPV infection because of recent initiation of sexual activity, but most infections regress spontaneously within a few years. This population would also not benefit from HPV DNA testing for any indication, including triage of ASC-US [25].

Pregnant women are screened at the same frequency as nonpregnant women; however, recommendations for management differ [14, 26]. Treatment of cervical neoplasia is deferred until after pregnancy (except in the case of invasive cancer) because of the risk to the unborn fetus and the low likelihood of progression to invasive disease [27].

Screening and treatment for cervical disease is recommended for HIV-infected women [14, 26, 28]. Among HIV-infected women, moderate and severe cervical dysplasia were designated as early symptomatic opportunistic infections and invasive cervical cancer as an AIDS-defining condition by the CDC in 1993. The CDC and IDSA recommend cervical screening twice (every 6 months) for the first year after initial HIV diagnosis and, if both test results are normal, annual screening thereafter.

Colposcopic evaluation is recommended by the CDC and IDSA for HIV-infected women with atypical squamous cells, cannot rule out a high-grade lesion (ASC-H), LSIL, or high grade squamous intraepithelial lesion on cytologic screening. Recommendations for management of ASC-US in HIV-infected women differ between ASCCP and the CDC and IDSA. ASCCP recommends HPV DNA test-based triage for colposcopy, whereas the CDC and IDSA recommend immediate colposcopic evaluation (no test-based triage) [14, 28].

Ongoing screening is not recommended for women with a history of total hysterectomy due to benign disease [29–31].

In summary, 2010 CDC guidelines for cervical screening in the STD clinic setting include the following:

- On the basis of high burden of HPV-related disease, clinics providing cervical screening services should use existing guidelines for age of initiating screening (≥ 21 years), intervals for screening (at least every 3 years), and age to discontinue screening (65–70 years).
- Clinics performing cervical screening should have protocols in place for referring women with abnormal test results for appropriate follow-up care.
- Bethesda 2001 guidelines should be used to report results of cervical cytologic tests.
- Newer technologies, including liquid-based cytology and HPV DNA testing, may be used as appropriate but should not be preferred over conventional testing methods (cytology alone), especially when resources are limited.
- If HPV DNA testing is included in screening, CLIA-certified laboratories should be used.
- Circumstances in which HPV DNA testing is not recommended include deciding about the need for HPV vaccination, screening to detect HPV for STD concerns, triage

for LSIL or higher, primary cervical cancer screening, and testing of women < 21 years of age.

- No preferential order for test specimen collection is recommended.
- Decisions on treatment of women with abnormal cervical screening test results should be based on existing guidelines, and women needing more intensive follow-up or treatment should be referred to facilities with more experience in managing abnormal cytologic test results (eg, colposcopy clinics).
- Cervical screening is recommended for pregnant women at similar intervals as nonpregnant women; however, management of test results may differ.
- Women with hysterectomy due to benign cervical disease are not recommended to receive cervical screening.
- More frequent cervical screening is recommended for HIV-infected women initially after HIV diagnosis. Management of abnormal screening tests may differ based on treatment of ASC-US.

Notes

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