

A PEER-REVIEWED ARTICLE

Human papilloma virus infections and disease in HIV

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Human papilloma virus (HPV) infection has been linked to both cervical and anal cancer and genital warts. HIV-infected individuals have been noted to have high frequencies of both these malignancies, as well as increased frequency of genital warts. HIV-infected women are more likely than non-HIV-infected women to have detectable levels of HPV DNA in cervicovaginal specimens,¹⁻⁶ squamous intraepithelial lesions (SIL), vulvovaginal condylomata acuminata, or anal intraepithelial neoplasia.⁶⁻⁹ The prevalence of SIL among HIV-infected women has been reported to range between approximately 12% and 40%¹⁰⁻¹¹ and adolescent HIV-infected women have particularly high prevalence rates of HPV infection (77.4%)¹² and SIL (55%).¹³

Among HIV-infected women, HPV disease, as manifested by findings of SIL or CIN (cervical intra-epithelial neoplasia) on cervical studies, is influenced by HIV-induced immune suppression. SIL and clinically-evident HPV infections have been associated with a declining CD4⁺ count.^{11,14-15} In addition, women with high plasma HIV RNA levels are at increased risk for cervical HPV infection with high-risk types and cervical cytologic abnormalities.^{11,16-17} However, cervical cancer has not shown such a dramatic relationship to lower CD4 cell counts.

Although most HIV-infected women with SIL present with low-grade lesions,^{1-2,7} SIL has been reported to be more severe and extensive in HIV-infected women compared with non-HIV-infected women and can present as multifocal extensive cervical and lower genital tract lesions.¹⁸ The increased incidence of HPV-related disease among HIV-infected women may be due to the high rate of persistent HPV infections, particularly among women with advanced immune suppression, with the oncogenic HPV types associated with the development of high-grade lesions and cervical cancer.¹⁹⁻²⁰

The risk of cervical disease progression among HIV-infected women with either low-grade SIL or type 1 CIN is relatively low. Observational studies have shown about 14% to 22% of women have cervical disease progress annually.¹⁹⁻²⁰ Only 20.6% of HIV-infected women with low-grade cervical dysplasia experienced progression to high-grade SIL in a randomized, observation-controlled clinical trial evaluating treatment with isotretinoin (median follow-up was 65 weeks for subjects on oral isotretinoin and 49 weeks for subjects on observation, n=102); the difference between the two arms was not significant.²⁵ In observational studies, progression of low-grade SIL has been associated with lower CD4⁺ counts and presence of HPV types 16, 18, and 33.^{24,26-27} The results from the one clinical trial and few observational studies suggest that observation without excisional therapy may be appropriate for HIV-infected women with low-grade SIL or type 1 CIN who are not prone to loss to followup. If treatment is recommended, loop electrosurgical excision procedure (LEEP) is a preferred treatment of CIN. HIV-infected women tolerate this procedure well with a low frequency of complications.²⁸ The relative low rate of HPV cervical infection that leads to pathological changes has prompted investigation into other risk factors for developing cervical dysplasia in HIV-infected women.

Invasive cervical carcinoma became an AIDS-defining diagnosis in 1993. The incidence is low among HIV-infected women, although the prevalence of SIL and CIN is high. In a large prospective study, the incidence of cervical cancer was not significantly higher among HIV-infected women compared to HIV-negative women (rate ratio 1.32, p = 0.80).²⁹ However, invasive cervical carcinoma is an important AIDS-defining illness and may be the most common AIDS-related malignancy among HIV-infected women in areas with a high prevalence of HPV infection.³⁰

Compared with non-HIV-infected women, HIV-infected women with invasive cervical carcinoma were likely to present with advanced clinical disease, have persistent or recurrent disease at follow-up, have a short time to recurrence, have a short survival after diagnosis, and die of cervical cancer.³¹ In the pre-HAART era, the median CD4⁺ count was relatively higher (153/mm³ versus 50/mm³) among women with invasive cervical carcinoma compared with women diagnosed with other opportunistic illnesses,³² but women with low CD4⁺ counts have a particularly poor prognosis.³³ Limited data on women with invasive cervical carcinoma in the post-HAART era have shown a better outcome. A review of malignancies in the HERS cohort found that women diagnosed with invasive cervical carcinoma had a higher mean CD4⁺ count (443/mm³) and, at time of publication, only one of four women had died of metastatic disease 55 months after diagnosis.³⁴ This is quite interesting that HIV-

infected women who develop cervical cancer are usually rather systemically immune intact in contrast to HPV genital infection and pre-cancerous lesions which are increased in women with lower CD4 cell counts.

Studies conducted in the United States, France, Italy, and Canada have had conflicting results regarding the impact of HAART on the persistence of HPV infection and cervical disease. Although some studies have shown that antiretroviral therapy seems to have a modest beneficial effect on the incidence of HPV infection and disease,^{14,35-36} other studies have not found an association between HAART and cervical disease regression (or progression).³⁷⁻³⁹

Because of the increased risk for cervical disease, in 1993 the CDC recommended HIV-infected women should have a Pap smear performed when found to be HIV infected; if normal, the Pap should be repeated in six months. Women who have never had an abnormal Pap smear and have had at least two normal Pap smears can undergo Pap screening every 12 months.⁴⁰⁻⁴¹ Although the risk for cervical HPV disease is lower among women with repeated normal Pap smears, one study showed 20% of HIV-infected women with no history of cervical disease developed biopsy-confirmed incident SIL within three years, highlighting the importance of relatively frequent cervical cancer screening in this population.⁴² If inflammation/atypia is present, a repeat Pap smear should be considered in three months, particularly if the woman does not have an infection to explain the results.⁴³ Routine baseline colposcopy screening is not recommended, but women with SIL, HPV findings, atypical squamous cells of uncertain significance (ASCUS), and atypical glandular cells (ACG) should be referred for colposcopy.^{40-41,43}

Among HIV-infected women, mild cytologic atypia⁴⁴ and atypical cells of undetermined significance⁴⁵⁻⁴⁶ are often associated with CIN. Women who do not have biopsy-confirmed CIN and who undergo an adequate colposcopic examination can be followed with repeat cytology in 12 months. Women with ASCUS should be referred back to colposcopy, but if two cervical screening examinations are negative, then the woman can have routine cytological screening. Women with ASG or low grade SIL who have an adequate colposcopy and who have no CIN lesions identified are recommended to have repeat cytological testing at six and twelve months.⁴⁰

Most of the literature pertaining to HPV disease has focused on cervical abnormalities, but anal infections are actually more common.⁴⁷ Several studies have also shown that anal cancer is increasing in HIV-infected individuals with the advent of HAART, probably because of the prolonged life span due to therapy. Guidelines from the CDC and NIH state "Although formal guidelines recommending anal Pap smear screening have not been adopted, certain specialists recommend anal cytologic screening for HIV-infected men and women. High-resolution anoscopy should be considered if the anal Pap smear indicates ASCUS or ASC-H and should be performed if a person has LSIL or HSIL on anal Pap smear. Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer." Clinicians should also inquire about symptoms such as anal itching, bleeding, diarrhea, or pain, and perform a visual inspection of the anal region and a digital rectal as a part of the physical examination. Ideally anal cytology should be performed at baseline and annually in MSM, women with a history of anal warts, women with abnormal cervical or vulvar histopathology, and women with abnormal Pap smears.⁴⁷ The challenge to these recommendations is the lack of infrastructure to perform and treat abnormal anal findings in most clinics. In addition, routine screening for AIN has not been shown to reduce the incidence of anal cancer.

Unlike for HIV-negative women, there are no current recommendations for the use of HPV testing to triage HIV-infected women with normal cytology to determine less or more frequent cytological screening evaluations or to determine the optimal follow-up of CIN after treatment. The use of HPV testing has been recommended to assist in management of HIV-infected women with ASCUS. The HPV vaccine is not contraindicated in HIV-infected adolescent and adult women and may be used in situations where the clinician believes it may offer clinical benefit.⁴¹ In many cases, the HIV-infected woman is very sexually experienced, making the available HPV prophylactic vaccine potentially less effective.

Several issues need to be clarified regarding use of the vaccine in HIV-infected persons. It is unknown whether or not HIV-infected individuals can mount and maintain protective antibody titers against HPV and whether the vaccine protects against anal HPV infection and AIN. The question of vaccinating men has also been raised to prevent penile infection and subsequent transmission to their partners.

In conclusion, cervical and anal cancers should be preventable with appropriate screening and follow-up. Additional risk factors or co-factors are likely involved in the development of cervical cancer even in this high-risk population. The HPV vaccine is an important contribution to prevention strategies but additional studies are warranted in the HIV-infected population.❖

EDITOR'S NOTE: This article is adapted from the chapter on HIV-infected women in Mandell's Principles and Practice of Infectious Disease (in press) to which Dr. Clark is a contributor.

REFERENCES

1. Sun XW, Ellerbrock TV, Lungu O, *et al*. Human papillomavirus infection in human immunodeficiency virus-seropositive women. *Obstet Gynecol*. 1995;85:680-686.
2. Vermund SH, Kelley KF, Klein RS, *et al*. High risk of human papillomavirus infection and cervical squamous intraepithelial lesions among women with symptomatic human immunodeficiency virus infection. *Am J Obstet Gynecol*. 1991;165:392-400.
3. Hillemanns P, Ellerbrock TV, McPhillips S, *et al*. Prevalence of anal human papillomavirus infection and anal cytologic abnormalities in HIV-seropositive women. *AIDS*. 1996;10:1641-1647.
4. Laga M, Icenogle JP, Marsella R, *et al*. Genital papillomavirus infection and cervical dysplasia—opportunistic complications of HIV infection. *Int J Cancer*. 1992;50:45-48.
5. Chaisson MA, Ellerbrock TV, Bush TJ, *et al*. Increased prevalence of vulvovaginal condyloma and vulvar intraepithelial neoplasia in women infected with the human immunodeficiency virus. *Obstet Gynecol*. 1997;89:690-694.
6. Kreiss JK, Kiviat NB, Plummer FA, *et al*. Human immunodeficiency virus, human papillomavirus, and cervical intraepithelial neoplasia in Nairobi prostitutes. *Sex Transm Dis*. 1992;19:54-59.
7. Wright TC, Ellerbrock TV, Chaisson MA, *et al*. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: Prevalence, risk factors, and validity of Papanicolaou smears. New York Cervical Disease Study. *Obstet Gynecol*. 1994;84:591-597.
8. Williams AB, Darragh TM, Vranizan K, *et al*. Anal and cervical human papillomavirus infection and risk of anal and cervical abnormalities in human immunodeficiency virus-infected women. *Obstet Gynecol*. 1994;83:205-211.
9. Korn A, Landers DV. Gynecological disease in women infected with human immunodeficiency virus type 1. *J Acquir Immune Defic Syndr*. 1995;9:361-370.
10. Sha BE, Benson CA, Pottage JC, *et al*. HIV infection in women: An observational study of clinical characteristics, disease progression, and survival for a cohort of women in Chicago. *J Acquir Immune Defic Syndr*. 1995;8:486-495.
11. Massad LS, Riestler KA, Anastos KM, *et al*. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. *J Acquir Immune Defic Syndr*. 1999;21:33-41.
12. Moscicki AB, Ellenberg JH, Vermund SH, *et al*. Prevalence of and risks for cervical human papillomavirus infection and squamous intraepithelial lesions in adolescent girls: Impact of infection with human immunodeficiency virus. *Arch Pediatr Adolesc Med*. 2000;154:127-134.
13. Fuller C, Clark RA, Kissinger P, *et al*. Clinical manifestations of infection with human immunodeficiency virus among adolescents in Louisiana. *J Adolesc Health*. 1996;18:422-428.
14. Delmas MC, Larsen C, Van Benthem B, *et al*. Cervical squamous intraepithelial lesions in HIV-infected women: Prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. *AIDS*. 2000;18:1775-1784.
15. Maiman M, Tarricone N, Vieira J, *et al*. Colposcopic evaluation of HIV infected women. *Obstet Gynecol*. 1991;78:84-88.
16. Luque A, Demeter L, Reichman R. Association of human papillomavirus infection and disease with magnitude of human immunodeficiency virus type 1 (HIV-1) RNA plasma level among women with HIV-1 infection. *J Infect Dis*. 1999;179:1405-1409.
17. Massad LS, Riestler KA, Anastos KM, *et al*. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. Women's Interagency HIV Study Group. *J Acquir Immune Defic Syndr*. 1999;21:33-41.
18. Centers for Disease Control: Risk for cervical disease in HIV infected women—New York City. *MMWR Morbid Mortal Wkly Rep*. 1990;39:846-849.
19. Sun XW, Kuhn L, Ellerbrock TV, *et al*. Human papillomavirus infection in women infected with human immunodeficiency virus. *N Engl J Med*. 1997;337:1343-1349.
20. Ahdieh L, Klein RS, Burk R, *et al*. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis*. 2001;184:682-690.
21. Belafsky P, Clark RA, Kissinger P, *et al*. Natural history of low-grade squamous intraepithelial lesions in women infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1996;11:511-512.
22. Biggers SD, LaGuardia KD. The natural history of low grade squamous intraepithelial lesions of the cervix in women with human immunodeficiency virus infection: Evidence for an algorithm for management. Abstract no. Th.B.4138. Presented at Eleventh International Conference on AIDS. Vancouver, Canada, 1996.
23. Olaitan A, Mocroft A, McCarthy K, *et al*. Cervical abnormality and sexually transmitted disease screening in human immunodeficiency virus-positive women. *Obstet Gynecol*. 1997;89:71-75.
24. Six C, Heard I, Bergeron C, *et al*. Comparative prevalence, incidence and short-term prognosis of cervical squamous intraepithelial lesions amongst HIV-positive and HIV-negative women. *AIDS*. 1998;12:1047-1056.
25. Robinson WR, Andersen J, Darragh TM, *et al*. Isotretinoin for low-grade cervical dysplasia in human immunodeficiency virus-infected women. *Obstet Gynecol*. 2002;99:777-784.
26. Massad LS, Ahdieh L, Benning L, *et al*. Evolution of cervical abnormalities among women with HIV-1: Evidence from surveillance cytology in the women's interagency HIV study. *J Acquir Immune Defic Syndr*. 2001;27:432-442.
27. Nappi L, Carriero C, Bettocchi S, Herrero J, Vimercati A, Putigano G: Cervical squamous intraepithelial lesions of low-grade in HIV-infected women: recurrence, persistence, and progression, in treated and untreated women. *Eur J Obstet Gynecol Reprod Biol*, 2005;121(2):226-32.
28. Kietpeerakool C, Srisomboon J, Suprasert P, *et al*. Outcomes of loop electrosurgical excision procedure for cervical neoplasia in human immunodeficiency virus-infected women. *Int J Gynecol Cancer* 2006;16:1082-88
29. Massad LS, Seaberg EC, Watts DH, *et al*. Long-term incidence of cervical cancer in women with human immunodeficiency virus. *Cancer* 2009;115:524-30
30. Maiman M, Fuchter RG, Clark M, *et al*. Cervical cancer as an AIDS-defining illness. *Obstet Gynecol*. 1997;89:76-80.
31. Maiman M, Fruchter RG, Serur E, *et al*. Human immunodeficiency virus infection and cervical neoplasia. *Gynecol Oncol*. 1990;38:377-382.
32. Klevens RM, Fleming PL, Mays MA, *et al*. Characteristics of women with AIDS and invasive cervical cancer. *Obstet Gynecol*. 1996;88:269-273.
33. Maiman M, Fruchter RG, Guy L, *et al*. Human immunodeficiency virus infection and invasive cervical carcinoma. *Cancer*. 1993;71:402-406.
34. Phelps RM, Smith DK, Heilig CM, *et al*. Cancer incidence in women with or at risk for HIV. *Int J Cancer*. 2001;94:753-757.
35. Luque AE, Li H, Demeter LM, *et al*. Effect of antiretroviral therapy on human papillomavirus infection and disease among HIV-infected women (abstract no. 724). *Conf Retroviruses Opportunistic Infect*. 2001;8:262
36. Heard I, Potard V, Costagliola D. Limited impact of immunosuppression and HAART on the incidence of cervical squamous intraepithelial lesions in HIV-positive women. *Antiretroviral Therapy* 2006;11:1091-6.

37. Lillo FB, Ferrari D, Veglia F, *et al.* Human papillomavirus infection and associated cervical disease in human immunodeficiency virus-infected women: Effect of highly active antiretroviral therapy. *J Infect Dis.* 2001;184:547-551.
38. Duerr A, Jamieson D, Cu-Uvin S, *et al.* Effect of highly active antiretroviral therapies on Pap smear abnormalities. Abstract no. MoPeB2245. Presented at the Thirteenth International Conference on AIDS, Durban, South Africa, July 9-14, 2000.
39. Money D, Hankins C, Rachlis A, *et al.* HAART and evolution of abnormal cervical cytology in women with HIV. Abstract WePeB5969. Presented at Fourteenth International AIDS Conference, Barcelona, Spain, 2002.
40. Centers for Disease Control. Sexually transmitted diseases treatment guidelines 2006. *MMWR Morbid Mortal Wkly Rep.* 2006;55(RR11):1-94.
41. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents @ <http://aidsinfo.nih.gov>, accessed 8/15/08.
42. Ellerbrock TV, Chiasson MA, Bush TJ, *et al.* Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA.* 2000;283:1031-1037.
43. Centers for Disease Control. 1993 Sexually transmitted diseases treatment guidelines. *MMWR Morbid Mortal Wkly Rep.* 1993;42(RR14):14.
44. Wright TC, Moscarella RD, Dole P, *et al.* Significance of mild cytologic atypia in women infected with human immunodeficiency virus. *Obstet Gynecol.* 1996;87:515-519.
45. Holcomb K, Abulafia O, Matthews RP, *et al.* The significance of ASCUS cytology in HIV-positive women. *Gynecol Oncol.* 1999;75:118-121.
46. Duerr A, Paramsothy P, Jamieson DJ *et al.* Effect of HIV infection on atypical squamous cells of undetermined significance. *Clin Infect Dis* 2006;42:855-61.
47. International AIDS Society. *Topics in HIV Med* 15:130-33

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