Lower Genital Tract Neoplasia in Women With HIV Infection

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Women who are infected with human immunodeficiency virus (HIV) are at greater risk for the development of lower genital tract neoplasia than are HIV-negative women. Among HIV-positive women, those who are more

Introduction

There has been a great deal of good news about the acquired immune deficiency syndrome (AIDS) during the last few years. Overall, the number of AIDS-related deaths has declined.[1] Due to the successful use of protease inhibitors combined with antiretroviral agents, the life expectancy for many people living with human immunodeficiency virus (HIV) is expected to be greatly extended and their quality of life improved. Use of the antiretroviral zidovudine (Retrovir) has reduced the transmission of HIV from mother to infant from 25% to 8%.[2] Finally, a study of (HIV serostatus discordant) couples has revealed that condoms are an effective method of preventing heterosexual transmission of HIV.[3]

The news about women has not been all good, however. The proportion of women accounting for new AIDS cases rose from 7% in 1985 to 20% in 1996.[1] Deaths due to AIDS in 1996 decreased by 15% among men but increased by 3% among women.[1] Although infants born to HIV-infected women who used zidovudine during pregnancy are less likely to be infected with HIV, the long-term consequences of zidovudine use for women and their infants are still poorly understood. In addition, single antiretroviral drug therapy is no longer the standard of HIV care; nonetheless, combination HIV therapies have not been fully evaluated in pregnant women. Lastly, although the male condom has been found to effectively prevent the transmission of HIV, there still are no effective preventive methods that are solely under the control of women.

The epidemiologic picture of HIV/AIDS in women also differs from the picture in men. The number of AIDS cases is highest among white homosexual men in the United States.[1] In contrast, women with AIDS are more likely to be nonwhite (75%) and to acquire the disease from intravenous drug use (34%) or heterosexual intercourse (40%). Cases of woman-to-woman transmission have been documented[4,5] but the total number of cases is unknown because this is not a transmission category that must be reported to the Centers for Disease Control and Prevention (CDC).

Women who become infected with HIV are likely to be socioeconomically disadvantaged, as well as disenfranchised from the health-care system. Unfortunately, women have either been invisible during the AIDS epidemic[6] or they have been unfairly characterized as vectors (eg, prostitutes) or vessels (eg, during pregnancy) of disease.

Another way in which the AIDS epidemic has affected women differently than men relates to the unique clinical manifestations of HIV disease. Of these, perhaps the most important manifestation in women with HIV is lower genital tract neoplasia. In this article, we will review the current body of knowledge about lower genital tract neoplasia in HIV-infected women.

Human Papillomavirus Infection in HIV-Infected Women

Human papillomavirus (HPV) is a double-stranded, circular DNA virus that can infect the stratified squamous epithelium of the lower genital tract, where it can exist in a dormant state, undergo replication (usually producing genital warts), or transform the host DNA, leading to uncontrolled cell growth. More than 80 types of HPV have been identified, about 15% of which infect the lower genital tract. These are divided into high- and low-risk types according to their degree of association with cervical cancer.
About 75% of invasive cervical cancers are associated with high-risk HPV types (subtypes 16, 18, 31, or 45) and less than 10% with low-risk types (subtypes 6 or 11). Low-grade cervical intraepithelial neoplasia (CIN) is associated with low-risk HPV types in 30% to 40% of cases and with high-risk types in < 20% of cases.[7]

Human papillomavirus infections are extremely common. Among young men and women in the United States, 60% have had prior HPV infection, 10% harbor subclinical infection detectable only by DNA testing, 4% have infection detectable by cytology or colposcopic examination, and 1% have grossly visible tumors. Only a very small proportion of HPV-positive women will develop invasive cancers of the lower genital tract. It is likely that HPV infection is necessary but not sufficient to produce lower genital tract malignancy. Possible cofactors leading to malignancy include tobacco smoking, other genital tract infections, and immunosuppression.

The association of HIV and HPV is not surprising since both viruses are sexually transmissible. Furthermore, since lower genital tract neoplasia has been associated with iatrogenic immunosuppression (such as after organ transplantation), the increased prevalence of HPV-related neoplasia among women with HIV immunosuppression is to be expected.

There seems to be an increased prevalence of lower genital tract neoplasia among HIV-infected women even when they are not immunosuppressed. Wright et al reported an increased risk for CIN due to HIV infection even after they controlled for the presence of HPV, immunosuppression, age, drug use, and various factors related to sexual activity.[8] Several studies have shown an increased detection rate of HPV DNA from the genital tract of HIV-infected women.

The human immunodeficiency virus may directly interact with HPV. For example, in vitro, HIV-1 transactivator [\texttt{tat}] protein enhances HPV E2-dependent transcription of HPV-16.[9] However, in vivo, HIV and HPV do not appear to coinfect the same cells; HIV is found mostly in monocytic cells, while HPV is found in squamous mucosal cells.[10] In the absence of immunosuppression, the interaction between HIV and HPV remains unexplained.

**Course of HPV Infection**

Among persons infected with HPV, immunosuppression, as measured by CD4+ cell counts, results in an increased proportion of CIN (replicating and integrated HPV infection) and a decreased proportion of latent HPV infections. The ratio of CIN to latent infection is 8:1 in the general population ([HIV-negative]), as compared with ratios of 3:1 in HIV-positive individuals with CD4 cell counts > 500/mm³ and 1:1 in those with CD4 counts < 200/mm³.[11]

Human immunodeficiency virus-infected women with high-grade CIN seem to be infected with different types of HPV than are HIV-negative women. Sun et al found that HPV types 16 and 18 predominated in HIV-negative women, while HPV types [30s] and [50s] were more common in the HIV-infected group.[11]

Moreover, HIV-infected women seem to shed HPV more frequently than HIV-negative women.[12] Semiquantitative DNA testing has shown a higher HPV viral load in some cervicovaginal lavage specimens obtained from HIV-positive than from their HIV-negative counterparts.[13]

In summary, HIV and HPV seem to be interactive infections. Most of the available evidence suggests significant differences in the course of HPV in women infected with HIV. As more research is done in this area, there are likely to be significant advances in our understanding of the pathophysiology of HPV infections.

**Lower Genital Tract Neoplasia**

Cervical intraepithelial neoplasia, also known as cervical dysplasia or squamous intraepithelial lesions (SILs), is common in women with HIV. In a review of 21 studies, five of which were controlled studies, Mandelblatt et al found that the odds of HIV-infected women having CIN was 4.9 times (95%
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confidence interval [CI], 3.0 to 8.2) greater than that of HIV-negative women.[14] The prevalence of CIN among HIV-infected women ranges from 31% to 63%. [13,15-20]

By analyzing Pap smears obtained from women before and after HIV seroconversion, Provencher et al demonstrated the development of abnormal cellular changes after seroconversion. They found that 12% of the smears were abnormal before seroconversion, as compared with 60% after seroconversion.[16]

In addition to having a higher prevalence of cervical dysplasia, women who are HIV-positive have larger lesions, more advanced CIN, and more vulvovaginal lesions than do HIV-negative women.[21]

Cervical Dysplasia and the Degree of Immunosuppression

There appears to be a relationship between the development of CIN and the degree of immunosuppression. For instance, women with symptomatic HIV infection are more likely to have CIN than are those with asymptomatic HIV infection.[13,18,22] In addition, the degree of immunosuppression (as measured by CD4+ cell counts) is correlated with an increased frequency of CIN among women with HIV.[19,23,24] This relationship between HIV immunosuppression and the development of CIN is not a surprising, as an increased incidence of CIN and cervical cancer has also been reported in other groups of immunosuppressed women, such as renal transplant recipients.[25]

Adequacy of Pap Tests in Detecting Cervical Dysplasia

Some researchers and clinicians have questioned whether Pap smears are an adequate method of detecting CIN in women with HIV. In an uncontrolled study, Maiman et al found that only 1 of 13 CIN lesions in HIV-infected women were detected by Pap smears.[18] Most of the subsequent studies have found that Pap smears have adequate sensitivity and specificity to detect CIN in women with HIV (Table 1).[8,26,27]

Although Pap smears may be adequate for screening, minor abnormalities on Pap smears may be more significant in HIV-positive than in HIV-negative women. Wright et al found that 38% of the HIV-positive women who had atypia on Pap smears had coexistent CIN detected by colposcopy, as compared with 14% of the women who were HIV-negative.[28] Based on these data, the current recommendations are to screen HIV-positive women every 6 months with a Pap smear and refer for colposcopy any woman who has atypia or CIN on her Pap smear.[29]

Multifocal Lower Genital Tract Neoplasia

Women with HIV are more likely to have multifocal lower genital tract neoplasia than are women without HIV. In addition to the cervix, neoplastic lesions are commonly found in other sites, such as the vagina and vulva. In one study with a small sample size (N = 19), 90% of the HIV-infected women had lesions on the vulva or perineum.[15]

Moreover, intraepithelial neoplasia in the vagina and on the vulva may not always be accompanied by cervical lesions in HIV-infected women. We found that 15% of 52 HIV-infected women who were examined by colposcopy had vulvar lesions in the absence of cervical lesions.[27]

Although the rate of multifocal disease has been found to range between 28% to 50% in women with HIV,[30] some of these small studies probably exaggerated the prevalence of multifocal disease due to selection bias. In a large, well-controlled study, vulvar and/or vaginal condyloma acuminata were detected in 5.6% (22/396) of the HIV-positive women but in only 0.8% (3/375) of the HIV-negative women.[31] High-grade SILs were found only in the HIV-positive women (N = 2).

In comparison to HIV-negative women, the prevalence of vulvar and vaginal lesions appears to be higher among HIV-positive women. We found that HIV-positive women were 27 times more likely to have vulvar intraepithelial neoplasia (VIN) than were HIV-negative women.[32]

This increased risk for VIN among HIV-infected women raises concern about the potential development of vulvar cancer. In fact, cases of invasive vulvar carcinoma have been documented in
women with HIV.[33] Since VIN is more common among women with HIV and may occur in the absence of CIN, Pap smears alone may not be adequate as a screening method. Colposcopy may be the most efficient method of detecting these lesions and may be especially warranted in HIV-positive women with a history of dysplasia or with vaginal or vulvar condylomata.

The finding of anal cancers in homosexual men with HIV[34] has led to the screening of HIV-infected women for anal intraepithelial neoplasia (AIN). In most cases, the performance of anal Pap smears has been done in conjunction with studies of the natural history of HIV. These studies have revealed that women with HIV are also at increased risk for anal dysplasia.[35] Cytologic abnormalities of the anus were detected in 26% of 27 HIV-infected women and 6% of 6 uninfected women.[36] Of the smears in the HIV-infected women, 5% were low-grade AIN. These data point to the need for increased vigilance in the detection of SILs throughout the lower anogenital tract.

**Recurrence or Persistence of Neoplasia After Therapy**

Lower genital tract neoplasia is more likely to recur or persist after treatment in HIV-positive than in HIV-negative women. Maiman and colleagues reported a 39% rate of recurrence of CIN following ablative or excisional therapy in HIV-infected women, as compared with a 9% recurrence rate in HIV-uninfected women.[37]

Wright et al found that 56% (19/34) of women with HIV who underwent loop electrosurgical excision had recurrent or persistent CIN, as opposed to 13% (10/80) of women with unknown HIV status.[38] In addition, the rate of recurrence/persistence was greater in the women who had CD4 counts < 200 cells/mm³, although this difference was not statistically significant.

In a prospective study that followed HIV-infected women for 18 months, persistent CIN was noted in 95% (18/19) of the women who did not receive treatment and in 61% (8/13) of the women who were treated.[39] Among women who had initially presented with low-grade CIN, cervical dysplasia persisted in 60% of the cases, which is twice the rate reported for the general population.[40]

We found that HIV-positive women who had VIN had a relative risk of recurrence or persistence of vulvar dysplasia of 3.3 (95% CI, 1.4 to 7.4; P = .01) after therapy, as compared with women who said that they were not HIV-infected.[32] The type of treatment, laser or excision, did not affect the rate of recurrence or persistence of VIN in either group.

Despite the common recurrence of intraepithelial neoplasia after treatment, reports of the development of invasive cancer in HIV-infected women receiving treatment are quite rare.

**Therapy and Monitoring for Intraepithelial Neoplasia**

Few studies have explored the effectiveness of treatment of intraepithelial neoplasia in women who are immunocompromised. More information is needed about the long-term effectiveness of various treatments, as well as the effect of the new combination therapies on the progression or regression of SILs. Additional therapies are needed that are effective against multifocal disease, are more effective against recurrent or persistent disease, do not affect future fertility, and are not disfiguring.

Little is known about how often women with HIV should be monitored for intraepithelial neoplasia with Pap smears or colposcopy. Long-term monitoring can be burdensome for some women and may affect follow-up.[P. D. Abercrombie, unpublished dissertation, 1997] As women live longer with HIV, noncervical lower anogenital tract cancers (especially vulvar and anal cancers) may become increasingly common. In women with iatrogenic immunosuppression after organ transplantation, a 100-fold increase in vulvar cancer has been reported, occurring after an average of 107 months.[41]

**Lower Genital Tract Cancer**

Cervical cancer may be the most common malignancy among women with AIDS.[42] Based on data from the CDC, the incidence of cervical cancer is about 900 per 100,000 among women with AIDS, as compared with about 10 per 100,000 among the general population.[43] In addition to cervical
cancer, other malignancies of the reproductive tract have been reported in HIV-infected women; these include ovarian tumors[44,45] and a cervical teratoma.[46] In some clinical settings, invasive cervical cancer is strongly associated with HIV infection. For example in Brooklyn, New York, 19% (16/84) of women with invasive cervical cancer were HIV-positive.[47]

Not only are women with HIV more likely to acquire cervical cancer, but also the clinical course of the disease may be worsened by concomitant infection with HIV. Compared with HIV-negative women, HIV-positive women with cervical cancer were more likely to be diagnosed at a later stage, have a poorer response to therapy, and have a higher rate of recurrence.[37] Similarly, cervical cancer among women with HIV can be rapidly progressive.[48,49] As a result of these and other findings, the CDC expanded the case definition of AIDS to include invasive cervical cancer.[50]

Because of this association between the two diseases, we suggest that women with invasive cervical cancer be offered HIV testing if their serologic status is unknown.

**Conclusions and Recommendations**

It should be clear from this review that knowledge about the pathophysiology and clinical management of lower genital tract neoplasia in HIV-infected women is incomplete. More research is needed, but there are many difficulties inherent in conducting studies in this area.

Many associations with HIV infection may be confounded by such variables as socioeconomic factors, access to medical care, illicit drug use, and risky sexual behaviors. Current measures of immunosuppression (such as CD4+ cell count) are crude and may not accurately reflect immune status on the mucosal level. Finally, HIV-infected women can be very difficult to study over time. Adherence issues related to substance abuse, lack of transportation, child care, fear, coincident illnesses, and medical visits are commonly encountered in this population.

Women with HIV, especially those who are severely immunocompromised, are at greater risk for the development of lower genital tract neoplasia than are HIV-negative women. Cervical cancer is one of the most important AIDS-related malignancies in women. Cancer and intraepithelial neoplasia of the lower genital tract can be persistent, progressive, recurrent, and difficult to treat in women with HIV. The most effective method of treatment for SILs has not been determined.

Regular performance of cervical Pap smears, as described above, can be of critical importance. Careful examination of the entire lower genital tract of HIV-infected women is crucial, due to the multifocal nature of HPV-related neoplasms. Noncervical neoplasia may become increasingly problematic in HIV-positive women as more effective antiretroviral therapy results in women living for longer periods with some degree of immunosuppression. We recommend that women who have high-grade intraepithelial neoplasia or cervical cancer be offered testing for HIV infection.

Finally, it is important to convey a positive message to women who have HIV and intraepithelial neoplasia. Although we are not very successful in preventing recurrences, progression to invasive cancer during therapy is rare, and it is invasive cancer, not intraepithelial neoplasia, that can be life-threatening.

**References:**


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