Cervicovaginal screening in women with HIV infection: A need for increased vigilance?

Catherine A. Hankins, MD, MSc, CCFP, FRCPC; John A. Lamont, MD, FRCPC; Margaret A. Handley, BA, MPH

Objective: To review the current literature on cervical disease (dysplasia, cervical intraepithelial neoplasia [CIN] or carcinoma) in women with HIV infection and to assess recommendations for cervicovaginal screening in these patients.
Data sources: MEDLINE and AIDSLINE were searched for relevant articles published in English or French between January 1987 and February 1993, abstracts presented at international AIDS conferences from 1989 to 1993 were evaluated, and pertinent agencies and organizations were consulted.
Study selection: A total of 92 reports of gynecologic disease in women with HIV infection were examined; 32 studies were retained that reported pertinent findings on cervical dysplasia, CIN or cervical carcinoma.
Data extraction: The following criteria were used to extract data: study design (descriptive v. comparative), sample size, heterogeneity of the study population, presence of immunodeficiency indicators (i.e., absolute CD4+ lymphocyte count) and presence of concomitant vaginal infections. Recommendations were assessed for their specific application to women with HIV infection.
Data synthesis: Data on the associations between stage of cervical disease and response to treatment at varying levels of CD4+ lymphocyte depletion were incomplete. Recommendations by official bodies for cervicovaginal screening in women with HIV infection differed little from recommendations for standard care of all women of reproductive age.
Conclusions: The consequences of a missed or delayed diagnosis of cervical disease for women with HIV infection can be severe. Pending further research, more frequent cervicovaginal screening through Papanicolaou testing and colposcopy in women with HIV infection is warranted.

Objectif : Examiner les publications courantes sur les maladies du col (dysplasie, néoplasie cervicale intraépithéliale [NCI] ou carcinome) chez des femmes infectées par le VIH et évaluer les recommandations relatives au dépistage cervico-vaginal chez ces patientes.
Sources de données : On a cherché dans MEDLINE et AIDSLINE des articles pertinents publiés en anglais ou en français entre janvier 1987 et février 1993, évalué des résumés présentés à l'occasion de conférences internationales sur le SIDA entre 1989 et 1993 et consulté des agences et des organismes compétents.
Sélection d'études : On a examiné au total 92 rapports sur des maladies gynécologiques chez les femmes infectées par le VIH et retenu 32 études qui ont fait état de constatations pertinentes sur la dysplasie cervicale, la NCI ou le carcinome du col.

Dr. Hankins and Ms. Handley are in the Centre for AIDS Studies, Montreal Regional Public Health Team, Montreal General Hospital, Montreal, Que., and Dr. Lamont is in the Department of Obstetrics and Gynaecology, Henderson General Hospital and McMaster University, Hamilton, Ont.

Reprint requests to: Dr. Catherine A. Hankins, Centre for AIDS Studies, Montreal Regional Public Health Team, Public Health Unit, Montreal General Hospital, 980 Guy St., Montreal, PQ H3H 2K3

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Extraction de données : On a utilisé les critères suivants pour extraire les données : conception de l'étude (descriptive ou comparative), taille de l'échantillon, hétérogénéité de la population visée par l'étude, présence d'indicateurs d'immunodéficience (c.-à-d. numération absolue des lymphocytes CD4+) et présence d'infections vaginales concomitantes. On a évalué l'application spécifique des recommandations aux femmes infectées par le VIH.
Synthèse des données : Les données sur les liens entre le stade de la maladie cervicale et la réaction au traitement à divers niveaux d'épuisement des lymphocytes CD4+ étaient incomplètes. Les recommandations formulées par des organismes officiels à l'égard des tests de dépistage cervico-vaginal chez les femmes infectées par le VIH différaient peu des recommandations relatives aux soins normaux chez toutes les femmes en âge de procréer.
Conclusions : Une maladie cervicale omise ou diagnostiquée en retard chez des femmes infectées par le VIH peut avoir de graves conséquences. En attendant des recherches plus poussées, des examens cervico-vaginaux plus fréquents à l'aide du test de Papanicolaou et de la colposcopie chez les femmes infectées par le VIH sont justifiés.

The recent addition of invasive cervical cancer in the presence of HIV infection to the list of illnesses that define AIDS cases in Canada[1] emphasizes the relation between HIV infection and cervical disease (dysplasia, cervical intraepithelial neoplasia [CIN] or carcinoma). Many women with HIV infection in Canada are under the care of specialists who may not routinely perform gynecologic examinations. Since cervical dysplasia, CIN and cervical carcinoma are often asymptomatic, clinical management must be changed to include regular cervicovaginal cytologic screening to lengthen the lives of women with HIV infection. To date, few organizations have formally assessed the need for tailored gynecologic care for women with HIV infection or made specific recommendations for follow-up. This review examines the scientific literature and the adequacy of current recommendations concerning cervicovaginal screening in women with HIV infection. At issue are the frequency of screening and the roles of the Papanicolaou smear, colposcopy and colposcopically directed biopsy in the assessment, treatment and follow-up of cervical disease associated with HIV infection.

In 1992 cervical carcinoma was the 10th most common cancer among women in Canada, with an estimated 1450 new cases and an incidence rate of 10.5 per 100 000 women.[2] In aboriginal populations cancer of the cervix may play a greater role; from 1967 to 1986 it ranked first among types of cancer in women who were registered Indians in Saskatchewan,[3] and from 1969 to 1988 it ranked second, after lung cancer, in Canadian Inuit women.[4]

The age-standardized incidence rate of cervical cancer among Canadian women declined on average 3% annually from 1981 to 1987,[2] but this trend was less marked among those 25 to 34 years of age, whose incidence rate was 11 per 100 000 women from 1986 to 1988.[5]

There are an estimated 3000 women with HIV infection in Canada[6] who are at increased risk for cervical disease. As many as 75% of women known to have HIV infection experience significant gynecologic problems.[7–11] Of particular concern are research findings suggesting that HIV-induced immunodeficiency can lead to CIN or cervical carcinoma by facilitating the expression of a causal agent.[12–15] The agent most often implicated is the human papillomavirus (HPV).[12,16] It is unclear whether acquiring HPV and HIV sequentially or concomitantly affects the onset of cervical disease. Further research is needed to determine how HIV-related immune suppression contributes independently to the progression of cervical disease.

The HIV epidemic could reverse the encouraging decline in the incidence rate of cervical cancer observed during the past decade in Canada. Such a reversal has been noted in some areas of the United States where latent HIV infection and HPV infection are highly prevalent,[17] the greatest increases in incidence rates occurring among women 20 to 39 years of age.[18]

Since invasive cervical carcinoma can be prevented through early detection and appropriate treatment of cervical disease, and since standard approaches to diagnosing and treating carcinoma may not succeed in women with HIV infection, tailored cervicovaginal screening of women with HIV infection merits exploration.

Methods

MEDLINE and AIDSLINE were searched with the use of appropriate MeSH terms to obtain relevant articles published in English or French from January 1987 to February 1993. In addition, abstracts from international AIDS conferences held from 1989 to 1993 were evaluated. Pertinent agencies and organizations in Canada and the United States were consulted to discover whether they had made or planned to make formal recommendations.

Of 92 studies of gynecologic disease in women with HIV infection we reviewed 32 that reported specific findings regarding cervical dysplasia, CIN, cervical carcinoma or more than one of these conditions.

Criteria used in extracting data were study design (descriptive v. comparative), sample size, heterogeneity of the study population, presence of indicators of immunodeficiency (absolute CD4+ lymphocyte count) and presence of concomitant vaginal infections. Information was grouped into three categories: prevalence of HPV in

relation to CD4+ lymphocyte count, clinical course of cervical disease in women with HIV infection, and comparative diagnostic performance of cytologic and histologic examination. Special attention was paid to studies that used sensitive polymerase chain reaction techniques to detect HPV and to prospective rather than cross-sectional studies of the clinical course of cervical disease. Recommendations were assessed for their specific application to women with HIV infection.

Results

Research review

Among women with HIV infection the prevalence of HPV infection varies depending on whether the HIV infection is asymptomatic or symptomatic. Three studies using various techniques to detect HPV infection showed that its prevalence in North America was similar among women without HIV infection and among those with asymptomatic HIV infection (20% to 27%).[13,15,19] In contrast, the reported prevalence among women with symptomatic HIV infection was as high as 79%.[13,15,19–21] In one study involving women with HIV infection a CD4+ lymphocyte count of 500×10^6/L or less was associated with an increased HPV prevalence: 59% (72/123) of women with a CD4+ count of 500×10^6/L or less had detectable HPV infection, as compared with 40% (23/58) of those with a count greater than 500×10^6/L ($p = 0.018$).[22] Thus, the prevalence of HPV infection among women with HIV infection appears to be inversely related to the degree of immunodeficiency, although whether this effect is continuous or has a threshold is not yet established.

HPV infection has been associated with cervical disease in women regardless of HIV status.[12,23] However, preliminary research has shown that in women with HIV infection HPV-related disease may progress faster and regress slower than in women without HIV infection.[24–27] Studies that reported CD4+ lymphocyte counts showed that this effect appears to be exacerbated by HIV-related immunodeficiency.[22,25] The current hypothesis that such immune suppression mediates the expression of a sexually transmitted causal agent such as HPV is supported by previous studies that showed an increased incidence of cervical cancer among women with immune suppression unrelated to HIV infection.[12,23,28]

Cervical dysplasia and cervical carcinoma in situ clearly may progress to invasive cervical cancer in the presence of HIV-related immune dysfunction.[29,30] Also, occult HIV-related immunodeficiency has been associated with fulminant cervical carcinoma in women without any other signs of immune suppression.[17] Regardless of whether immunodeficiency is present higher rates of multifocal cervical disease, of multiple sites and of perianal involvement have been reported among women with HIV infection than among women without such infection.[17] Just as Kaposi's sarcoma in patients with AIDS differs from that in transplant patients,[31] fulminant forms of cervical disease, necessitating aggressive management and treatment, may emerge as a result of HIV infection. In particular, there are reports of unusual metastatic patterns that do not respond to standard treatments of squamous cell cervical cancer in women with HIV infection.[32,33] Cancer recurrence rates as high as 69% after cervical conization[34] and response rates as low as 20% after cryotherapy[35] underscore the need for new therapeutic approaches to cervical dysplasia, CIN and cervical carcinoma in such women. Women with cervical disease and HIV infection also have higher recurrence and death rates as well as shorter intervals before recurrence and death than women with cervical disease alone; this underscores the importance of detecting cervical neoplasia in the preinvasive stage in women with HIV infection.[17] As a further challenge to clinical management, the diagnosis of intermediate stages of cervical dysplasia can be complicated by severe vaginal infections,[36] which are common in some populations of women with HIV infection.

The role of specific types of HPV in the development of anogenital cancer in women with HIV infection has not been studied extensively. HPV 16, 18, 31, 33, 35, 45 and 51 as well as other rare types (e.g., HPV 39, 40, 52 and 56) have been associated with high-grade CIN and invasive cervical cancer in women without known HIV infection.[23,37,38] In a study involving 192 women with HIV infection and 187 control patients in New York, researchers, using sensitive polymerase chain reaction techniques, found the overall HPV prevalence to be 52% and 22% respectively and the HPV 18 prevalence to be 29% and 7% respectively ($p < 0.001$).[22] The prevalence of aggressive types of HPV in Canadian women is unknown; however, a study now under way in nine cities across the country will establish the prevalence of HPV types in women with HIV infection and investigate the relation between HPV type and HIV infection, immune suppression and cervical disease.[39]

Some studies based on small samples have shown that cervical cytologic testing in women with HIV infection may not reveal dysplasia detectable by colposcopy or colposcopically directed biopsy.[17,40–44] In a study involving 32 women with HIV infection Papanicolaou testing revealed only 1 woman (3%) with CIN, whereas colposcopy identified 13 (41%) with CIN.[45] Although they found interreader variability in assessing cytology specimens from women with HIV infection to be low, Fink and associates,[44] in evaluating 51 women with HIV infection, reported positive results of Papanicolaou testing for 46% and of colposcopy for 89% of the 18 with CIN histologically proven by biopsy.

False-negative results of Papanicolaou testing in women with HIV infection are more likely in the presence of vaginal disease caused by *Neisseria gonorrhoeae*, *Chlamydia*, herpes simplex virus, *Candida* and

Trichomonas vaginalis.[40] Most of the studies comparing Papanicolaou test sensitivity in women with and without HIV infection did not report the prevalence of concurrent infections.[42,43] One study that did not control for the presence of vaginal infections showed no significant difference in the proportion of false-negative cytologic results in women with HIV infection and in those without it. Overall, Papanicolaou test results were false negative in 30.4% of the 69 women studied.[42] The high proportion of false-negative results[46] is a serious concern, since the consequences of a missed diagnosis of cervical disease are likely to be more severe for women with HIV infection than for those without it.

Review of current recommendations

Few gynecologists' associations or organizations representing women's health concerns have considered the clinical issues concerning women with HIV infection or made formal recommendations on the frequency of Papanicolaou testing and colposcopy in such women. Also, specific criteria for measuring immune function (e.g., CD4+ lymphocyte count or the onset of illnesses including AIDS-defining diseases) have not been incorporated in recommendations for cytologic or colposcopic examination and follow-up in these women.

In 1990 the US Centers for Disease Control and Prevention (CDCP), Atlanta, published guidelines recommending annual Papanicolaou testing in women with HIV infection as long as specimens were adequate for interpretation and results were normal.[47] These recommendations did not differ from those for standard care of all women of reproductive age; they have since been modified to include a repeat screening 6 months after the initial test to rule out false-negative results.[48] If both Papanicolaou smears yield normal results, screening reverts to an annual schedule. In addition to expanding the AIDS surveillance case definition to include invasive cervical carcinoma, the CDCP has placed cervical carcinoma in situ as well as moderate and severe cervical dysplasia in a category of conditions that are AIDS defining if the CD4+ lymphocyte count is less than 200 $\times$ 10^6/L.[36] Canada has not yet followed suit, since it has added only invasive cervical carcinoma to its revised definition.[1] Nevertheless, the apparent discordance between existing recommendations for screening and the revised AIDS case surveillance definitions in Canada and the United States, in conjunction with current knowledge concerning HIV infection and cervical disease, suggests that more aggressive screening should be recommended.

Although it has not made a formal recommendation the American College of Obstetricians and Gynecologists (ACOG) has stated that semiannual Papanicolaou testing should be performed in women with HIV infection, who are likely to be followed up semiannually in any case because of their HIV infection.[48]

The routine use of colposcopy to screen women with HIV infection has not been strongly supported for logistic, ethical and cost-related reasons. The CDCP stated recently that HIV infection is not an indication for colposcopy.[48] The Society of Obstetricians and Gynaecologists of Canada (SOGC) has not declared whether an exception for women with HIV infection should be made to its 1981 statement that "colposcopy has no role in the screening of patients for premalignant or occult invasive disease of the cervix and therefore it does not serve as the initial means of identifying patients with such disease."[49] Its US counterpart, the ACOG, said that liberal recourse to colposcopy may be appropriate when Papanicolaou smears in women with HIV infection are uninterpretable or yield abnormal results, even if only koilocytes or inflammation are found.[48] In contrast, the CDCP recommends only a repeat Papanicolaou smear in 3 months if the initial smear reveals severe inflammation or reactive squamous cell changes.[47]

The Canadian community-based patient advocacy organization AIDS Action Now! generally agrees with the ACOG in recommending routine Papanicolaou testing in women with HIV infection each 6 months, to be followed by colposcopy if the results suggest HPV infection.[50] However, this organization goes one step further by advocating that for women with a CD4+ count below 200 $\times$ 10^6/L Papanicolaou testing should be done every 3 months and colposcopy every 6 months, the latter being done more frequently if the smear results suggest HPV infection.

The paucity of formal recommendations and lack of consensus on screening frequencies and techniques have led to wide variations in practice. Recommendations to clinicians concerning the nature and timing of follow-up of women with HIV infection should be based on scientific outcomes. Consequently, more research into the clinical manifestations of HIV infection in women, particularly gynecologic disease, is needed to provide conclusive data and to guide clinical management. In the meantime, the critical need for early detection of cervical lesions in women with HIV infection must be weighed against patient convenience and compliance.

Conclusion

Stronger recommendations for the screening of cervical disease in women with HIV infection are justified in light of the findings that cervical dysplasia, CIN and cervical carcinoma in such women have a more fulminant course and may be more refractory to standard treatments than in women without HIV infection. Furthermore, we question the appropriateness of only annual screening in women at increased risk for concurrent gynecologic infections, since such infections may increase the prevalence of false-negative or uninterpretable results from a Papanicolaou smear.[40] Finally, the poor sensitivity of Papanicolaou testing lends support to

recommending baseline colposcopic screening as the CD4+ lymphocyte count begins to fall. Family physicians, obstetricians, gynecologists and internists who care for women with HIV infection should consider our recommendations based on CD4+ lymphocyte counts (Table 1).

We believe that the standard recommendations for annual cervicovaginal screening should apply as long as the CD4+ count is high and the Papanicolaou test results are adequate. If unable to obtain the CD4+ lymphocyte count physicians and their patients may choose Papanicolaou testing every 6 months. Screening for and treatment of vaginal infections in women with HIV infection is important because Papanicolaou smears are more likely to yield false-negative or uninterpretable results in the presence of such infections.

Regardless of the CD4+ lymphocyte count, cervical dysplasia detected through Papanicolaou testing, including mild dysplasia with koilocytotic or condylomatous atypia indicating HPV infection, should be followed up with colposcopic examination guided by acetic acid visualization and, if indicated, colposcopically directed biopsy. Cervical dysplasia should be aggressively treated with the use of appropriate cryotherapy, electrodesiccation or laser therapy.

Our recommendations are based on the current scientific evidence. Their implementation may be limited by the lack of colposcopy services in Canada for women with HIV infection. As well, patient compliance with colposcopy may be problematic. Some referral clinics have significant no-show rates among women without known HIV infection; women with HIV infection may be less compliant, particularly during the asymptomatic stage, or more compliant if they are encouraged to consider the value of gynecologic care to their overall health. Further studies are needed to determine which factors encourage or inhibit compliance with colposcopic examination for all women; such studies will be particularly valuable for women with HIV infection, who are at increased risk of cervical carcinoma. Studies are also needed to determine the cost effectiveness of applying these recommendations to the estimated 3000 women with HIV infection in Canada and the effect of the recommendations on the quality of life and survival of these women.

Table 1: Recommendations for cervicovaginal screening in women with HIV infection

CD4+ lymphocyte count > 500 cells $\times 10^6$/L
Annual cervicovaginal cytologic examination if initial Papanicolaou smear and repeat smear at 6 months are adequate and yield negative results
CD4+ lymphocyte count 200–500 $\times 10^6$/L
Cervicovaginal cytologic examination every 6 months and annual colposcopic examination*
CD4+ lymphocyte count < 200 $\times 10^6$/L
Cervicovaginal cytologic examination every 3 months and colposcopic examination every 6 months*

*Colposcopic examination should be guided by acetic acid visualization.

At present, few laboratories in Canada can determine the exact type of HPV present, and any HPV typing currently taking place has a strong research rather than clinical focus. It will be increasingly important in the coming years to determine which HPV types are most aggressive in the presence of HIV infection and whether the virulence of these types differs from that observed in women without HIV infection. Such research may prove useful in drafting recommendations in the future, when technologic advancements in the handling, transport and testing of specimens allow local practitioners to conduct HPV typing.

Finally, research into the association between stage of cervical disease and response to treatment at varying CD4+ lymphocyte counts is incomplete. Trials of single or combination treatments involving women with HIV infection at varying levels of immune suppression are needed to determine optimal approaches to therapy.

Despite these gaps in research, which should be addressed, the evidence warrants changes to the standards of gynecologic care of Canadian women with HIV infection.

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