Management of Cervical Neoplasia in Human Immunodeficiency Virus-Infected Women

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The existence of cervical neoplasia in women with human immunodeficiency virus (HIV) represents one of the most serious challenges in the oncologic care of immunosuppressed patients. While the development of most cancers in the immunosuppressed patient can be attributed solely to immune deficiency, the relationship between squamous cell neoplasia of the cervix and HIV is quite unique because of common sexual behavioral risk factors. Screening strategies in HIV-positive women must take into account the high prevalence of cervical dysplasia in this subgroup as well as the limitations of cytologic screening. Cervical dysplasia in HIV-positive women may be of higher grade than in HIV-negative patients, with more extensive involvement of the lower genital tract with HPV-associated lesions. The presence and severity of cervical neoplasia in HIV-positive women correlate with both quantitative and qualitative T-cell function. Standard therapies for preinvasive cervical disease have yielded suboptimal results with high recurrence rates. While poor treatment results of standard ablative and excisional therapies warrant unique therapeutic strategies, one must recognize that close surveillance and repetitive treatment have been successful in preventing progressive neoplasia and invasive cervical carcinoma. The disease characteristics of invasive cervical carcinoma may take a more aggressive clinical course in HIV-infected women. HIV-positive women with cervical cancer have higher recurrence and death rates with shorter intervals to recurrence and death than do HIV-negative control subjects. CD4 status does influence subsequent outcome. In general, the same principles that guide the oncologic management of cervical cancer in immunocompetent patients should be applied. However, extremely close monitoring for both therapeutic efficacy and unusual toxicity must be instituted. [Monogr Natl Cancer Inst 1998;23:43–49]

Human immunodeficiency virus (HIV) infection continues to be a national and international health problem of epidemic proportions. Despite the fact that new acquired immunodeficiency syndrome (AIDS) cases increased by less than 5% for the fifth year in a row, a number well below the rate of increase in the epidemic’s first decade, the incidence of AIDS cases among women continues to increase, particularly in minority women. Approximately 19% of new adult and adolescent cases of AIDS in the United States last year were in women, and women represent the subgroup with the greatest rate of increase compared with any other defined population in North America. As with cervical neoplasia, HIV infection is largely a disease of women in their reproductive years, with the incidence of both diseases significantly higher in women of color.

The existence of cervical neoplasia in women infected with HIV represents one of the most serious challenges in the oncologic care of immunosuppressed patients. While the development of most illnesses and cancers in HIV-infected patients can largely be attributed to immune deficiency, the relationship between cervical neoplasia and HIV infection is quite unique. Both cervical carcinoma and HIV infection are, in part, sexually transmitted diseases, with oncogenic types of human papillomavirus (HPV) infection the implicated viral carcinogen associated with cervical cancer. Therefore, an association between cervical cancer and HIV can be anticipated not only on the basis of immunosuppression but also because of shared common sexual behavioral risk factors. Thus, while immunosuppressed women, such as renal transplant patients receiving highly immunosuppressive drugs, are known to be at high risk for lower genital tract neoplasia, immunodeficient HIV-infected women are perhaps the highest risk subgroup that we know of. While these factors likely play the major role in the pathogenesis of cervical neoplasia in HIV-infected women, direct interactions between HIV and HPV at the molecular level, the effects of HIV on the local mucosal immune response, enhancement of HPV regulatory expression by the HIV-1 tat protein, and HIV-induced perturbations of paracrine or autocrine factors that influence HPV gene expression must also be considered.

Screening Issues

Because a well-defined precursor lesion for cervical cancer can be detected by screening, organized screening programs for cervical neoplasia can be expected to reduce both the incidence and the mortality rates. Since the prevalence of disease is far greater in HIV-positive patients than in the general population, optimal screening strategies take on an increased importance. HIV-positive women have as much as a 10-fold increased rate of abnormal cytology, including a wide range of cellular and inflammatory changes, such as hyperkeratosis, parakeratosis, trichomonas, herpes, inflammatory atypia, HPV-related changes, and varying degrees of cervical neoplasia (1). Higher rates of abnormalities have also been demonstrated after seroconversion than before seroconversion. Studies from several centers have demonstrated that women who are immunodeficient from HIV infection have cytologic abnormality rates of between 30% and 60% (2–4) and Pap smears consistent with

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cervical dysplasia from 15% to 40% (5). Most studies also consistently demonstrate that the prevalence of such abnormalities increases as immunodeficiency becomes more severe.

Screening strategies in HIV-positive women must take into account the high prevalence of cervical dysplasia in this subgroup as well as the limitations of cytologic screening, the relatively high noncompliance rate, and the possibility of accelerated progression of disease. These factors make initial accurate diagnosis critical. Although the Centers for Disease Control and Prevention (CDC) continues to recommend Pap smears as the sole screening method, many authors have advocated the need for baseline colposcopy in HIV-infected women because of the inaccuracy of cytology in consistently predicting histology, low negative predictive values of the Pap smear, decreased sensitivity, and discordances between cytologic smear and biopsy results (6–10). Other authors have found that HIV-infected women had significantly more smears of limited adequacy due to obscuring blood or inflammation and higher rates of concomitant vaginal infections leading to under-read smears (11). Maiman et al. (12) in a unique study of 248 HIV-infected women, all of whom had cytology, colposcopy, and biopsy, found that 38% of all cervical intraepithelial neoplasia (CIN) in 13% of the total patients would have been missed if routine colposcopy and biopsy were not performed. Interestingly, similar high false-negative rates of cytology have been reported in immunosuppressed women after renal transplantation (13).

The limitations of cytologic screening become more glaring as the prevalence of cervical dysplasia increases in a given population. Although more frequent cytologic screening (every 6 months) is to be advocated, a reasonable but not universally accepted approach that we use at our institution involves baseline colposcopy or cervicography in HIV-positive women once the diagnosis is made (Fig. 1). Patients with normal colposcopy could then undergo more aggressive cytologic screening than the normal population, while those diagnosed and treated for CIN undergo colposcopy with liberal biopsy every 4–6 months for 2 years and semianual Pap tests thereafter. Alternatively, screening strategies may be based on baseline immune status, with more aggressive techniques reserved for patients with CD4 counts of less than 500/mm³. Of course, all strategies must take into account availability of colposcopic resources and individualized knowledge of risk in given patient populations.

In contrast to the inherent lack of sensitivity of normal cervical cytology, abnormal cytology is extremely accurate in predicting CIN on histology, and Pap smears indicating CIN must be taken very seriously (14). Specificities of 84% or greater have been reported with even higher predictive values (10). Therefore, the vast majority of such patients will indeed have cervical pathology, justifying immediate treatment during initial colposcopic evaluation of a significantly abnormal Pap smear. This “see-and-treat” approach using excisional methods such as the loop electro surgical excision procedure may be particularly appropriate for the HIV-infected woman.

The prevalence of HIV infection in women with invasive cervical carcinoma may be even higher than in those with preinvasive disease. Maiman et al. (15) reported a 19% seropositivity rate in women under the age of 50 years in a high-risk population in Brooklyn. Of course, this high prevalence rate is, in fact, reflective of the high HIV infection rate in our community and would be expectedly lower in lower risk geographic areas. Most important, the majority of these women were asymptomatic with regard to HIV disease and die of cervical cancer, not AIDS; therefore, only HIV screening programs would have detected their positive serostatus. At our institution, we currently recommend HIV counseling and testing in all younger (<50 years of age) patients with cervical cancer, since test results may have a significant impact on oncologic therapeutic strategies. The Gynecologic Oncology Group (GOG) is currently conducting a nationwide screening study involving HIV testing and follow-up of newly diagnosed patients with invasive cervical carcinoma.

**Invasive Cervical Carcinoma**

On January 1, 1993, the CDC expanded the surveillance case definition of AIDS to include...
HIV-positive women with invasive cervical cancer. As an AIDS-defining illness, it is required that physicians and hospitals report cases of cervical cancer in HIV-infected women to their local health departments. These changes have served to educate the health care community concerning this relationship and stimulate more aggressive testing programs. In the first year of the expanded definition, approximately 1.3% of women with AIDS-defining illnesses 13 years of age or older had cervical cancer (16). However, HIV testing in women with cervical cancer was far from routine, and documentation of AIDS cases varied considerably based on the reporting practices of physicians and hospitals. Other factors may also contribute to the underdiagnosis of cervical cancer in HIV-infected women, including lack of HIV testing in older women, poor access to health care, and the coexistence of more acute and life-threatening AIDS-defining opportunistic infections that inhibit both the diagnosis and the reporting of cervical cancer. In an urban population at high risk for both diseases in Brooklyn, where a routine HIV testing program was instituted in all cervical cancer patients 50 years of age or younger (17), cervical cancer was the sixth most common AIDS-defining illness in women representing 4% of the subjects as well as the most common AIDS-related cancer in women (55%), followed by lymphoma (29%) and Kaposi’s sarcoma (16%).

The signs and symptoms of cervical cancer may take on typical or atypical presentations in HIV-infected women. Ideally, patients should be diagnosed by classic screening methods of cytology, colposcopy, and biopsy if disease is to be detected in the preinvasive or early invasive phase. When patients present with symptoms, more advanced disease is often found, and vaginal bleeding or postcoital bleeding is most commonly reported. Malodorous vaginal discharge is also quite common, as is pelvic pain, back pain, or lower abdominal pain. Leg pain, edema, weight loss, or obstructive uropathy is indicative of more advanced disease. In HIV-positive patients, metastatic disease may occur in both common and uncommon sites (18), and unusual extracervical metastases have been described in the psoas muscles, pericervical area, and spinal cord as well as malignant ascites (19,20). Diagnosis can be even more difficult, because the classic signs of systemic cancer may mimic the subtle manifestations of HIV disease. Low-grade fevers, unexplained weight loss, gastrointestinal disturbances, and fatigue may occur in both disease processes. Lymphadenopathy, either clinically detected in the left supraclavicular (scalene) or inguinal nodes, or retroperitoneal (pelvic or para-aortic) nodes, discovered at the time of surgery or radiologic imaging, must not be assumed to be metastatic cancer; HIV-infected patients will often have very large, suspicious nodes that may be secondary to follicular hyperplasia, not to a tumor. This pathologic diagnosis, which includes mononuclear cell proliferation, polykaryocytes, epithelioid histiocytes, and mantle-zone loss, while not pathognomonic for HIV, is highly suggestive.

In addition, coexistent pelvic infection may present diagnostic and therapeutic dilemmas. HIV-infected women have high rates of concomitant pelvic inflammatory disease that is more often refractory to antibiotic therapy. Pelvic abscesses may mimic metastatic cervical cancer and pelvic infection may contribute to the development and spread of disease and increase the failure rate and morbidity of therapeutic interventions.

Cervical cancer is the only gynecologic cancer that is clinically staged, which is assigned by the current staging system of the International Federation of Gynecology and Obstetrics (FIGO). Once a clinical stage is assigned and treatment has been initiated, the stage must not be changed because of subsequent findings by either extended clinical or surgical staging. Bimanual rectovaginal pelvic examination, performed under anesthesia if necessary, is the most important part of clinical staging, and only certain additional studies for extracervical disease are allowed by FIGO, including intravenous pyelogram, barium enema, chest and skeletal x ray, cystoscopy, and sigmoidoscopy. However, other more practical and useful studies are often employed that provide more specific information, including computerized axial tomography, magnetic resonance imaging, and laparoscopic lymph node biopsies or extraperitoneal lymph node biopsies by laparotomy. Tumor markers, specifically squamous cell carcinoma antigen or CA 125 for the respective cell types of squamous or adenoscarcoma, are useful parameters to follow patients with during and after treatment.

Cancers of the cervix most often spread by direct invasion into the cervical stroma and laterally into the parametrial tissues as well as into the vagina and corpus uteri. Lymphatic metastases are also quite common and are involved in a progressive fashion beginning with the pelvic (oburator, external and internal iliac) nodes and then involving the para-aortic, inguinal, and scalene nodes. The incidence of positive pelvic and para-aortic nodes ranges from 15% to 5%, respectively, for patients with stage IB disease to 45% and 30% for patients with stage III. However, HIV-positive patients may have higher grade tumors and higher rates of lymph node involvement than expected by stage alone. Cervical cancer may also spread by blood-borne metastases or intraperitoneal implantation or present or recur with painful bony metastases.

Although much of the data, thus far, has been limited to case reports and single institution studies, it seems apparent that in some HIV-infected women, the disease characteristics may take a more aggressive clinical course (15,21). This parallels the examples observed in other AIDS-related cancers. HIV-positive women present with more advanced disease than do HIV-negative women with cervical cancer. In the largest study to date at the Health Science Center at Brooklyn comparing 16 seropositive to 68 seronegative women, significantly more advanced disease was found in the HIV-positive women (15). Half of the seropositive patients presented with stage III or IV disease, compared with 19% in seronegative controls, and only one infected patient remained with early disease after careful surgical–pathologic staging. Almost 70% of the HIV-infected women had stage III or higher surgical–pathologic stage compared with 28% of seronegative controls. HIV-infected women with cervical cancer may be quite young, such as the case of a 16-year-old who presented with stage IIB disease and died at age 17 years (18). Most HIV-positive patients can be expected to have squamous cell carcinomas as was found in the above study where 15 of 16 patients had squamous cell cancers, with the remaining patient having an adenosquamous tumor (15). Most important, the majority of patients die of cervical cancer before they died of AIDS and are usually asymptomatic with regard to HIV infection. Therefore, only HIV testing programs of such patients will...
enable the physician to make the diagnosis and realize the full impact of the interaction of these two disease processes.

The HIV-positive women with cervical cancer have higher recurrence and death rates with shorter intervals to recurrence and death than do HIV-negative control subjects (15). Mean intervals to recurrence are extremely short, and many patients retain persistent disease after primary treatment. Median time to death was found to be 10 months in seropositive women compared with 23 months in seronegative patients. Several other case reports have described examples of rapidly progressive cervical cancer in such women. As with preinvasive disease, the relationship between immune function and disease status is apparent. The mean absolute CD4 count in such patients was 360/mm³ compared with 830/mm³ in uninfected women. One can infer from these values that the typical HIV-infected woman with cervical cancer would not meet the immunologic definition for AIDS solely by CD4 count (<200/mm³), emphasizing the importance of the recent inclusion of seropositive women with cervical cancer as AIDS patients. Although stage of cancer may not predict CD4 levels, immune status does influence subsequent outcome. Patients with counts greater than 500/mm³ have had more favorable disease courses; therefore, management decisions in HIV-infected women with cervical cancer should carefully consider pretreatment immune function, since positive serostatus alone may not necessarily and uniformly confer a dismal outcome (15). HIV-related immunodeficiency may contribute heavily to the natural history of cervical carcinoma, and HIV-positive patients need not demonstrate other signs of immunosuppression such as opportunistic infections for their neoplasia to be adversely affected by HIV.

The characteristics of HIV disease in cervical cancer may be different in cervical cancer patients when compared with HIV-negative patients with other AIDS-related cancers. Women with invasive cervical cancer are less immunosuppressed than women with other AIDS opportunistic illnesses and may be expected to have CD4 counts about twice as high as those with Kaposi’s sarcoma and non-Hodgkin’s lymphoma (312–153/mm³) (17). In the majority of women with cervical cancer, HIV infection was diagnosed at the time of cancer presentation, whereas in women with other cancers, HIV diagnosis preceded cancer diagnosis by a mean of 2.7 years. Although the interval from cancer diagnosis to death may be similar in all AIDS-related cancers, cancer was found to be the cause of death more often with cervical cancer patients (95%) compared with those with other cancers (60%). Although patients with cervical cancer as their AIDS-defining illness may be slightly younger than those without cervical cancer, the distribution of mode of HIV transmission (heterosexual versus injection drug abuse) and race (black versus Hispanic versus white) was found to be remarkably similar (16).

The management of HIV-positive patients with cervical cancer is among the most challenging tasks faced by the oncologic team. In general, the same principles that guide the oncologic management of cervical cancer in immunocompetent patients should be applied (Fig. 2). However, extremely close monitoring for both therapeutic efficacy and unusual toxicity must be instituted.

Radical hysterectomy and pelvic lymphadenectomy should be performed in most cases of stage IA2 and IB1 and in some cases of stage IB2 and IIA cervical cancer where cervical size is not too enlarged and vaginal involvement is minimal. Radical oncologic surgery in HIV-positive women can be performed for the usual indications, and surgical decisions should be based on oncologic issues not HIV status. As has been demonstrated in other types of operations in the HIV-positive patients, women with relatively good immune function tolerate surgery well with no significant excess morbidity. Prophylactic antibiotics should be routinely used, and standard surgical precautions should be taken to prevent surgical transmission. The transmission rate of HIV from patient to health care worker is extremely low, estimated to be about 1 in 320.

Although radiation therapy can be used in all stages of cervical cancer and has identical cure rates when compared with radical surgery in stage IB, the issues of ovarian conservation and better vaginal sexual function make radical hysterectomy the preferred modality in younger patients. Ovarian transposition should be considered at the time of surgery if postoperative pelvic radiation is a strong possibility. One may expect a urologic fistula rate of 1%–2% and a chronic bladder atony rate of 3% after radical hysterectomy compared with an intestinal and urinary stricture and fistula rate of 3%–5% and rate of chronic radiation fibrosis of the bowel or bladder of 6%–8% with pelvic radiation therapy. Another advantage of surgery over radiation is the availability of surgical–pathologic data such as lymph node status for which postoperative therapy can then be designed.

Since most HIV-infected patients with cervical cancer present with more advanced disease, radiation therapy is usually the cornerstone of treatment and is the basis for therapy in stages II–IV. Pelvic radiation therapy begins with external-beam therapy designed to shrink the primary tumor and create better geometry for the brachytherapy insertions to follow. Pelvic fields are usually 15 × 5 cm, extending to a 2-cm margin lateral

**Stage Ia1:** Cold knife therapeutic cone biopsy if fertility desired; otherwise, simple hysterectomy

**Stage Ia2**

**Stage Ib1** Radical hysterectomy with pelvic lymphadenectomy
Alternative, radiation therapy in poor surgical candidates

**Stage Ib2**

**Stage Ia** Radiation therapy +/- simple hysterectomy; or Radical hysterectomy with pelvic lymphadenectomy; or Neoadjuvant chemotherapy + radical surgery

**Stage IIA-IVa:**
Radiation therapy +/- chemosensitization

**Stage IVb:**
Chemotherapy +/- radiation therapy

**Recurrent Disease:** Pelvic Exenteration (central disease), otherwise Palliative Chemotherapy

Fig. 2. Treatment recommendations for cervical carcinoma in human immunodeficiency virus-infected women.
to the bony pelvis and inferiorly to the border of the obturator foramen. The superior margin can be extended to 18 cm to cover the common iliac nodes or even higher if para-aortic lymph node metastases are evident. The usual dosages of pelvic radiotherapy delivered include 7000–8000 cGy to point A and 6000 cGy to point B. Some HIV-positive patients may respond poorly to radiation therapy alone and regimens that incorporate radiation sensitizers that are being used more frequently in general should be strongly considered. The two most common sensitizing regimens include cisplatin (50 mg/m², weeks 1 and 6) combined with fluorouracil (1000 mg/m², continuous infusion × 4 days, weeks 1 and 6) or oral hydroxyurea (3 g/m², twice per week × 5 weeks). One must also keep in mind that pelvic radiation is associated with transient lymphopenia and depressed T-cell function, which may lead to further immunologic compromise in the HIV-positive patient, and that anecdotal reports of poor tolerance and increased morbidity from pelvic radiation therapy have been made, although adequate studies have not yet been performed to evaluate this issue.

Chemotherapy should be used in cases of systemic disease (pulmonary or liver metastases) or recurrent disease after radiation failures in those patients not eligible for pelvic exenteration. However, recurrent cervical cancer in this setting is not considered curable with chemotherapy, and treatment is palliative. Regimens that incorporate drugs that are both active in cervical carcinoma and relatively bone marrow sparing should be used, with close monitoring of all hematologic indices. Cisplatin (50–75 mg/m²) is the drug of choice and may be combined with bleomycin (20 U/m²; maximum, 30 U) and vincristine (1 mg/m²). Recently, neoadjuvant chemotherapy has been used in patients with stage IB2 or stage II cervical cancer with similar agents followed by radical hysterectomy with good results; however, the efficacy of this approach in HIV-positive patients is unknown.

Other novel therapeutic approaches, such as the use of interferons, retinoids, bone marrow support, or vaccine therapy, may represent future investigative treatment options. The Gynecology Oncology Group is presently evaluating the role of interferon alfa and isotretinoin with or without antiretroviral therapy in the neoadjuvant or advanced/recurrent setting in the treatment of HIV-infected women with cervical cancer. Innovative treatment regimens and research protocols such as these are needed to combat the interaction of these two potentially life-threatening disease processes.

Last, the treatment of HIV and its sequelae with anti-HIV-1 agents and prophylactic regimens is exceedingly complex and always changing. Combination therapy with nucleoside analogues and protease inhibitors is now standard and initiated earlier in the course of HIV disease. Careful attention to overlapping side effects of these regimens when combined with oncologic therapy for cervical cancer as well as potential synergistic antineoplastic effects will be an important area of future investigation.

Preinvasive Cervical Neoplasia

HIV-seropositive women represent perhaps the highest risk group encountered for the development of CIN. In the most recent classification system of HIV-related diseases, the CDC has identified moderate to severe cervical dysplasia and carcinoma in situ as category B conditions. Independent studies (2,4,6,10) have estimated the prevalence of CIN in this subgroup to be between 20% and 50%. Maiman et al. (12), in a study of HIV-positive women without AIDS-defining illness, found the prevalence of CIN on histology to be 32% in a cohort of 248 patients. Cervical dysplasia of HIV-positive women may be of higher grade than in seronegative women, with more extensive involvement of the lower genital tract with HPV-associated lesions (18). Extensive cervical involvement, endocervical involvement, and multisite (vagina, vulva, and perianal) disease are more common. Natural history studies examining the biologic behavior of cervical HPV and CIN strongly suggest that disease is more aggressive in HIV-positive patients. Conti (22) found fourfold higher progressions and threefold lower regression rates of untreated HPV-related cervical lesions in infected women compared with HIV-negative controls, and Petry et al. (23) found only a 27% regression rate of CIN I lesions in immunosuppressed HIV-positive and transplant patients compared with 62% in immunocompetent control subjects. Higher rates of more oncogenic HPV subtype infection, multiple-type HPV infection, and unspecified-type HPV infection have been reported by many investigators and may help explain the more aggressive cervical pathology that develops in HIV-infected women (12,24–26).

Numerous studies (6,9,27) have demonstrated the relationship between HIV-associated immunosuppression and the development of CIN, and the presence and severity of cervical neoplasia are associated with quantitative T-cell function. In one study (6), HIV-positive patients with CIN had absolute CD4 counts and T4:T8 ratios roughly half those of HIV-positive patients without CIN, and patients with AIDS-defining illness are more likely to have cervical disease than are asymptomatic HIV-positive patients. Schafer et al. (27) and Wright et al. (28) concluded that a CD4 lymphocyte count of 200/mm³ was independently associated with CIN. The concept of worsening immunodeficiency increasing the risk of cervical pathology may be used to individualize screening and surveillance strategies in HIV-positive women.

The treatment of preinvasive cervical disease in HIV-infected women is among the most challenging and frustrating tasks faced by the practicing gynecologist. In general, standard therapeutic strategies for immunocompetent women apply, but the increased risk for treatment failures and chronic nature of disease in such women is well documented.

Excisional methods, which include LEEP (loop electrosurgical excision procedure), laser cone, and cold knife cone biopsy, are preferred over ablative methods, such as cryotherapy and laser vaporization. Excisional methods have the advantage of confirmation of histology and documentation of negative margins, which is of particular importance in HIV-positive women in whom disease may be more extensive. Del Priore et al. (29) reported that colposcopically directed biopsies may be poor predictors of histology on excisional cone specimens in HIV-seropositive women, since 47% with CIN II–III on cone biopsy had only CIN I or HPV on punch biopsy compared with only 9% in HIV-seronegative patients. Additionally, with advances in the technology in electrosurgical generators and the development of large wire loops with insulated bases, LEEP has allowed excision of the cervical transformation zone and distal canal with a
Recurrence rates for CIN in HIV-positive women with standard therapies have been reported to be as high as 40% at one year and 60% with longer follow-up (30,31). Maiman et al. (30) and Del Priore and Lurain (9) reported recurrence rates of 39% and 40%, respectively, compared with 9% and 10% on seropositive controls. Fruchter et al. (32), at 36 months, reported a 62% failure rate compared with 18% in control subjects, with an 87% failure rate in patients with CD4 less than 200/mm$^3$. In addition, progression to higher grade dysplasia was more common in HIV-positive patients as well as multiple episodes of recurrent disease requiring many repeated procedures. It has been well documented that the frequency of recurrence is closely related to immune function. Patients with CD4 counts less than 500/mm$^3$ are at extremely high risk for recurrence, whereas women with counts greater than 500/mm$^3$ may be expected to have a recurrence at only twice the rate of seronegative women (30). Therefore, diagnostic and therapeutic strategies may be stratified based on the degree of immunosuppression. Unfortunately, complications after treatment for CIN in HIV-positive women may be increased since one study demonstrated higher rates of excessive bleeding and cervicovaginal infections (33).

While poor treatment results of standard ablative and excisional therapies in HIV-infected women with CIN certainly warrant unique therapeutic strategies, one must recognize that close and meticulous post-therapy surveillance and repetitive aggressive re-treatment for persistent and recurrent disease have been successful in preventing progressive neoplasia and invasive cervical carcinoma and should therefore not be abandoned. Hysterectomy, which is rarely used today in the management of CIN in immunocompetent patients, may be considered in individual cases in HIV-seropositive women and be particularly reserved for the multiparous patient with relatively good immune function who has undergone multiple therapeutic procedures for recurrent high dysplasia in whom repeated evaluation is exceedingly difficult.

In response to the high rates of treatment failures for preinvasive cervical disease in HIV-positive women, the AIDS Clinical Trials Group (ACTG) is investigating novel therapeutic approaches. For patients with high-grade dysplasia (CIN-II–III), ACTG examined the role of topical vaginal fluorouracil cream maintenance therapy as prophylaxis against recurrent CIN. In this study, patients were randomized to receive standard ablative or excisional therapy alone versus standard therapy plus 2 g of vaginal fluorouracil every 2 weeks for 6 months. Fluorouracil has previously been used with considerable success in the care of immunocompromised women with lower genital tract neoplasia, especially after conventional therapy has resulted in repetitive recurrence. Krebs (34) found that prophylactic maintenance therapy with vaginal fluorouracil was effective in the treatment of HPV-associated lesions of the vulva and vagina, especially in immunosuppressed women with multiple organ involvement. Effective local adjunctive therapy with topical chemotherapeutic agents is particularly attractive in HIV-positive patients in light of their favorable therapeutic index, and results of such randomized controlled studies are extremely important.

ACTG 293 is a study involving the treatment of HIV-positive patients with CIN-I. While the standard of care today in immunocompetent women with CIN-I (mild dysplasia) is close follow-up without surgical therapy, it is unknown whether such conservative strategy is safe in seropositive patients in light of reports suggesting more aggressive disease. In this trial, patients are randomized between observation only without any surgical

![Fig. 3. Treatment options for cervical intraepithelial neoplasia in human immunodeficiency virus-positive women. S-FU = fluorouracil.](http://jncimono.oxfordjournals.org/)
therapy versus oral isotretinoin at a dose of 0.5 mg/kg per day for 6 months, with close attention to follow-up for regression, persistence, or progression. The results of this trial are likely to have implications for women with CIN in general.

Optimization of immune function and lowering of viral load with proven and newer anti-HIV drugs are also desirable, and many patients today are placed on multiple drug regimens. It is unknown whether any of such interventions has any impact on cervical disease, and the presence of multiple confounding variables will make this issue exceedingly difficult to study. At present, the principles of aggressive initial evaluation, more frequent cytologic screening, and meticulous post-therapy surveillance with liberal repeat colposcopy and re-treatment for recurrent dysplasia in managing preinvasive disease in HIV-infected women seem prudent as we investigate novel treatment strategies in clinical trials.

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