

Management of the Female HIV-Infected Patient

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ABSTRACT

Management of women with HIV infection or AIDS should follow the established guidelines for antiretroviral therapy and prevention and treatment of opportunistic complications of HIV infection. Gynecological manifestations of HIV are primarily cervical dysplasia and cancer associated with human papillomavirus (HPV) infection and vaginal and mucocutaneous candidiasis. Human papillomavirus-associated cervical dysplasia/neoplasia is more common in women with advanced rather than early HIV disease, and monitoring with Pap smears should probably increase to every 6 months in patients with CD4⁺ cell counts <500 cells/ μ l (and certainly when this value falls below 200), with positive Pap smears confirmed by colposcopy and biopsy. For patients with CD4⁺ cell counts >350 cells/ μ l, cryotherapy is probably adequate, but therapy should be increasingly aggressive at lower CD4⁺ cell counts. Results of ongoing studies should be available soon to guide therapy. Optimal treatment of candidiasis in HIV-infected women includes prevention of recurrence with a combination of topical and systemic antifungal agents. Women with child-bearing potential should be treated as medically indicated for other HIV-infected patients, including during pregnancy. In fact, preliminary results of ACTG 076 indicated that zidovudine therapy during pregnancy reduces vertical transmission of HIV about threefold.

IN ADDITION TO other issues in women's health,¹⁻³ pregnancy and HIV infection is an important area that must be addressed in discussions of management of HIV disease.^{4,5} Specific clinical presentations and conditions are found in women with HIV infection, depending on the stage of their immunosuppression.^{6,7} Gynecological manifestations of HIV are primarily (1) human papillomavirus (HPV) and cervical dysplasia and cancer⁸ and (2) initial presentation and management of vaginal and mucocutaneous *Candida* infection.⁹ The importance of HIV infection in pelvic inflammatory disease is being investigated.¹⁰

HUMAN PAPILLOMA VIRUS AND HIV

There are high rates of HPV infection and cervical dysplasia in women infected with HIV; however, it is not clear whether HIV infection and its associated immunosuppression precede or follow HPV infection and its consequences.¹¹⁻¹³ For example, in a study of 200 women,³ the most common viral infections were genital warts (32 patients) followed by herpes simplex

virus infections (28 patients), Epstein-Barr virus manifested as oral hairy leukoplakia (9 patients), and polydermatomal herpes zoster virus (8 patients). Genital warts in HIV-infected patients may be much more extensive and aggressive than is typical in nonimmunocompromised patients.

There is a clear association of HIV and cervical dysplasia/neoplasia, which is stronger in women with advanced rather than early HIV disease.¹⁴ Cytological findings from Pap smears in women with defined alterations in lymphocyte counts reveal increasing cervical dysplasia with decreasing CD4⁺ cell counts (see Table 1). In women with CD4⁺ cell counts less than 200 or 250 cells/ μ l, the incidence of dysplasia and invasive cancer is higher than in women with normal CD4⁺ cell counts or CD4⁺ cell counts >500 cells/ μ l.

There have been several case reports of rapidly progressive cervical cancer that did not respond to appropriate therapy (including radical surgery, radiation therapy, and chemotherapy) in HIV-infected women.¹⁵ This correlates with the degree of immune suppression.

Although concerns have been raised about the usefulness of Pap smears in HIV-infected women, leading to recommenda-

TABLE 1. CERVICAL CYTOLOGY AND CD4⁺ CELL COUNTS^a

| CD4 ⁺ count class ^b | No signs of dysplasia | Dysplasia | Invasive carcinoma | Total |
|---|-----------------------|-----------|--------------------|-------|
| T1 | 17 (70%) | 7 (30%) | — | 24 |
| T2 | 29 (62%) | 18 (38%) | 1 | 47 |
| T3 | 10 (48%) | 11 (52%) | — | 21 |
| T4 | 9 (47%) | 10 (53%) | 4 | 19 |
| Total: | 65 (59%) | 46 (41%) | 5 | 111 |

^aFrom Schafer *et al.*⁹

^bT1, No detectable change; T2, >400 cells/μl; T3, between 400 and 250 cells/μl; T4, <250 cells/μl.

tions of colposcopy and biopsy instead of Pap smears in all of these patients, studies have validated Pap smears in these patients.¹⁶ The Centers for Disease Control and Prevention (CDC, Atlanta, GA) recommend Pap smears every year for HIV-infected women.¹⁷ When the CD4⁺ cell count is <500 cells/μl, and especially when it is <200 cells/μl, screening should be more frequent (probably every 6 months). If cervical disease is found, colposcopy and biopsy are appropriate. Cryotherapy or cryosurgery is probably adequate in patients with CD4⁺ cell counts >350 cells/μl, depending on the severity of the lesion. In patients with lower CD4⁺ cell counts, especially <200 cells/μl, therapy should be more aggressive, with laser therapy and combination therapy with 5-fluorouracil and careful followup. Results of ongoing studies in this area should be available to guide therapy in the near future.

CANDIDIASIS

Vaginal candidiasis, a common manifestation of HIV infection in women (see Table 2), is often a clinically significant problem that may be recurrent and refractory to topical therapy and is the most frequent early sign of HIV disease among women seeking HIV antibody testing. In HIV-infected women, *Candida* vaginitis heralds a change in overall health and occurrence of other HIV-related conditions and often precedes oral thrush as a sign of HIV disease. Severity is closely related to the degree of immunosuppression as indicated by CD4⁺ cell count or the ratio of CD4⁺ to CD8⁺ cells. For example, mean CD4⁺ cell counts were 506 cells/μl in women with vaginal candidiasis only, and 230 cells/μl in women with oral candidiasis.⁹ Esophageal candidiasis typically occurs later in the course of infection.

Almost half of the women with previous vaginal *Candida* infections observed an increase in the frequency and severity of symptoms 6 months to 3 years prior to HIV testing.

In a study of 200 women with HIV infection,³ there were typically at least 4 discrete episodes of vaginal candidiasis per patient per year, or the frequency of episodes will have at least doubled. This provides guidance for primary practitioners in

(36 patients) and esophagitis (24 patients) as well as some cutaneous disease (7 patients). Only 15 of these patients had *Pneumocystis carinii* pneumonia (PCP), and only 2 patients had cryptococcal meningitis. The amount of *Candida* present is greatly increased in HIV-infected compared to non-HIV-infected women. Also, HIV *Candida* vaginitis typically includes the vulva, with cutaneous manifestations. Analysis of biopsy specimens often reveals evidence of invasive as well as superficial *Candida*.

The rates of *Candida* culture positivity and symptomatic *Candida* vulvovaginitis increase with immune compromise. Also, yeasts other than *Candida albicans* are isolated more frequently in HIV-infected women.¹⁸ In 134 HIV-positive women without AIDS-defining conditions compared with 292 HIV-negative women, the ability to culture *Candida* from vulvovaginitis increased dramatically (~20 times) when the CD4⁺ cell count was <100 cells/μl.

Although only limited clinical results comparing antifungal therapy for vulvovaginal candidiasis are available, it appears that symptomatic and mycological cure rates are similar with topical clotrimazole and oral itraconazole, whereas fluconazole was somewhat less effective in this trial (see Table 3).¹⁹

Response to therapy is usually good, but relapses frequently require retreatment or maintenance therapy in a majority of pa-

TABLE 2. INITIAL CLINICAL MANIFESTATIONS OF HIV INFECTION IN 177 WOMEN^a

| Condition | Number of patients (%) |
|--|------------------------|
| Vaginitis, <i>Candida</i> spp., recurrent | 43 (37%) |
| Lymphadenopathy | 17 (15%) |
| Bacterial pneumonia | 15 (13%) |
| Acute retroviral syndrome | 8 (7%) |
| Constitutional symptoms | 8 (7%) |
| Oropharyngitis, <i>Candida</i> spp. (thrush) | 6 (5%) |
| Purpura, thrombocytopenic | 6 (5%) |
| Oral hairy leukoplakia | 4 (3%) |
| Herpes zoster, multidermatomal | 2 (2%) |
| <i>Pneumocystis carinii</i> pneumonia (PCP) | 2 (2%) |

TABLE 3. CLINICAL RESPONSE TO THERAPY FOR ACUTE VULVOVAGINAL CANDIDIASIS^{a,b}

| | <i>Clotrimazole</i> (topical) | <i>Fluconazole</i> (one dose) | <i>Itraconazole</i> (two doses) |
|-------------------------|----------------------------------|----------------------------------|------------------------------------|
| Number treated | 82 | 72 | 75 |
| Clinical response | | | |
| No change | 6 (7.3%) | 6 (8.3%) | 6 (8.0%) |
| Improved | 10 (12.2%) | 21 (29.2%) | 9 (12.0%) |
| Cured | 66 (80.5%) | 45 (62.5%) | 60 (80.0%) |
| Mycological response | | | |
| <i>Candida</i> negative | 78 (95.1%) | 60 (83.3%) | 72 (96.0%) |
| <i>Candida</i> positive | 4 (4.9%) | 12 (16.7%) | 3 (4.0%) |

^aFrom Higgins *et al.*¹⁹

^bDosages: Clotrimazole (500 mg pessary plus 1% cream); fluconazole (150 mg as a single oral dose); and itraconazole (200 mg twice daily for 1 day).

tients.²⁰ Therefore, antifungal therapy needs to be aimed not only at treating the acute manifestations but also at preventing subsequent episodes. This requires a combination of topical and oral antifungal agents.

Prophylaxis with fluconazole (50 mg three times a week) is effective in preventing new instances of mucosal candidal infections in HIV-infected women with CD4⁺ cell counts <500 cells/ μ l.²¹

My personal tendency is to treat patients who have recurrent vaginal candidiasis with a short course of oral antifungal therapy (3 to 5 days of ketoconazole, 200 mg/day) followed by topical clotrimazole (500 mg intravaginally) weekly or monthly. In patients with lower CD4⁺ cell counts, oral therapy will probably be necessary.

Other specific manifestations of HIV infection in women include genital ulcerative disease, cervicitis, and salpingitis. Human papillomavirus infections (including the genital warts they often cause) are significantly more frequent and more difficult to treat and control in HIV-infected women. Optimal clinical management requires more frequent screening in patients with documented immunosuppression (decreased CD4⁺ cell counts) and aggressive treatment of viral, bacterial, and fungal infections.

HIV INFECTION IN PREGNANCY

Eighty percent of women with HIV infection in the United States are of child-bearing age. The frequency of HIV infection in women giving birth is approximately 1.5 per 1000, which leads to estimates of almost 6000 HIV-infected women giving birth annually in the United States.

Available data suggest that pregnancy has little effect on HIV disease progression per se.^{22,23} However, these are limited studies of asymptomatic women observed for relatively short periods. During pregnancy, the rate of decline in CD4⁺ cell counts was more rapid in HIV-positive women compared with HIV-negative women; however, little or no difference has been observed in the rates of clinical or immunological deterioration.

team approach that includes counseling and psychosocial support services. Patients should be screened for sexually transmitted diseases and other infectious agents including *Mycobacterium tuberculosis*, cytomegalovirus, *Toxoplasma gondii*, and HPV.

Low CD4⁺ cell counts have been shown to predict the development of serious infections in both pregnant and nonpregnant women.

Some routine invasive techniques (e.g., amniocentesis, umbilical cord blood sampling, and fetal scalp electrodes) should be avoided in HIV-infected women if possible. Breast-feeding should be discouraged.

Antiretroviral agents (e.g., zidovudine), antituberculous agents (e.g., isoniazid), and antibiotics for treatment or prevention of infections (e.g., penicillin and trimethoprim-sulfamethoxazole) should be used as appropriate in both pregnant and nonpregnant women.⁴ One study has suggested that zidovudine appeared to be safe and well tolerated without significant hematological abnormalities in both mothers and infants.²⁴ Most use of zidovudine has been after the first trimester of pregnancy. Appropriate prophylaxis should be provided to the mother, because disease is also being prevented in the infant.

Potential interruption of vertical transmission of HIV infection is an important issue²⁵ that has been evaluated by AIDS Clinical Trials Group (ACTG) 076, a study evaluating zidovudine in pregnant women with HIV infection.⁵ An interim review revealed a transmission rate of 8.3% when both mothers and infants received zidovudine compared with 25.5% among those receiving placebo. Therefore, enrollment has been stopped and all currently enrolled women are being offered zidovudine therapy. This includes therapy for the infant during the first 6 weeks of life. Another protocol, ACTG 185, to evaluate immune globulin has been designed but not yet activated.

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