Gynecologic conditions are common in women with HIV. HIV-positive (HIV+) women are significantly more likely than noninfected women to have prevalent and incident gynecologic disorders, but they are not more likely to develop conditions, such as sexually transmitted infections (STIs), related to risk-taking. In a study conducted by Minkoff et al of 262 HIV-infected women, serial assessment revealed that 46.9% of the women had at least 1 incident gynecologic condition. A separate study of women treated in an inpatient AIDS service reported that, although only 9% of the women were admitted for primary gynecologic diagnoses, on evaluation 83% were found to have a coexisting gynecologic disease.

Gynecologic conditions most commonly seen in HIV+ women include menstrual disorders, genital ulcer disease, vaginal infections, pelvic inflammatory disease, and human papilloma virus–related problems, including genital warts and lower genital tract dysplasia and neoplasia. In addition, choice of contraception in HIV+ women poses special challenges. Prevention of unintended pregnancy and HIV transmission must be considered along with potential drug-drug interactions. This article reviews these issues as well as routine gynecologic care of the HIV+ patient.
Management of selected gynecologic disorders in HIV+ women may differ from approaches used to treat the general population. Components of routine gynecologic care for HIV+ women require special consideration on the part of the clinician.

**Menstrual Disorders**

There is an extremely broad differential diagnosis for menstrual disorders in women with HIV. Higher viral loads and lower CD4 counts have been associated with increased cycle variability as well as with polynormorrhrea.3,4 Some studies have shown that HIV+ women also are more likely to experience longer menstrual cycle intervals (>6 weeks),4 and possibly an increased incidence of anovulation or premature menopause;6 however, a recent large study of HIV+ and high-risk HIV-negative (HIV-) women from the HIV Epidemiology Research Study (HERS) and the Women's Interagency HIV Study (WIHS) prospective cohorts found that HIV serostatus had little overall effect on amenorrhea or menstrual cycle length or variability; and other studies show little or no difference in the menstruation patterns of HIV+ women.3,4,7

When an HIV+ patient presents with either abnormal bleeding or amenorrhea, a first step is to test for pregnancy. Once pregnancy is ruled out, other potential causes can be explored (Table 1). Ovulatory disorders that may present with either amenorrhea or abnormal bleeding are common, particularly in women with advanced disease. Progestin-only methods of contraception, such as depot medroxyprogesterone acetate injections and levonorgestrel implants, often are associated with some irregular bleeding. Other confounding variables include substance abuse,8 weight loss, and chronic disease. Women who have received megestrol, a potent progestin, for appetite stimulation may present with irregular bleeding or spotting or with amenorrhea. Sometimes infection, particularly cervicitis or endometritis, may be a cause of abnormal bleeding. A systemic condition affecting coagulation also may present as vaginal bleeding, and thrombocytopenia also is more common in the setting of HIV.5,10

Although HIV-infected women frequently may experience menstrual dysfunction at some time during their illness, HIV infection alone is not a clear cause without the influence of these confounding variables. Evaluation of amenorrhea or abnormal bleeding in an HIV-infected woman should be performed similarly to that for the general population.11 Serum follicle-stimulating hormone and estradiol may be useful in making the diagnosis of menopause if this is suspected.11

**Genital Ulcer Disease**

Genital ulcers generally are infectious in etiology, most commonly secondary to herpes simplex virus (HSV) or syphilis, with chancroid a less common cause of genital ulceration in women in the United States. Genital ulcers increase the risk of HIV transmission or acquisition, but HIV also may affect the presentation or management of genital ulcers. HSV lesions may be atypical in appearance or location and outbreaks may be more frequent, prolonged, and/or severe with progressive immunosuppression; HSV viral shedding increases with declining CD4 counts12 and higher plasma HIV viral load.13 Plasma HIV viral load also is increased with HSV reactivation.14

HIV-infected women with HSV may require higher doses and/or longer courses of treatment with antivirals, especially in cases of more advanced immunosuppression. Suppressive therapy also may be beneficial.

HIV+ patients with syphilis may have abnormal serologic test results (eg, unusually high titers, false negatives, or delayed seroreactivity). However, serologic tests generally can be interpreted in the usual manner. If clinical findings suggest syphilis but serology is nonreactive, biopsy, darkfield examination, or direct fluorescent antibody staining of lesion material should be considered. The clinical presentation of syphilis is very variable at all stages; atypical manifestations may be seen in the setting of HIV infection. Neurosyphilis should be considered in the differential diagnosis of neurologic signs or symptoms that present in HIV-infected individuals.15

Compared with HIV- patients, HIV+ patients who have early-stage syphilis may be at increased risk for neurologic complications and may have higher rates of treatment failure with currently recommended regimens, which generally are similar for both populations; cerebrospinal fluid examination is recommended in

<table>
<thead>
<tr>
<th>Table 1. Potential Causes of Menstrual Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Anovulation/ovulatory disorders</td>
</tr>
<tr>
<td>• Hormonal contraception: DMPA, levonorgestrel implants</td>
</tr>
<tr>
<td>• Substance abuse</td>
</tr>
<tr>
<td>• Weight loss, chronic disease</td>
</tr>
<tr>
<td>• Infection: cervicitis, endometritis</td>
</tr>
<tr>
<td>• Uterine fibroids, polyps</td>
</tr>
<tr>
<td>• Neoplasia</td>
</tr>
<tr>
<td>• Endocrine disorder; thyroid dysfunction, PCOD</td>
</tr>
<tr>
<td>• Systemic coagulopathy: thrombocytopenia</td>
</tr>
<tr>
<td>• Other medications</td>
</tr>
</tbody>
</table>

DMPA = depot medroxyprogesterone acetate; PCOD = polycystic ovarian disease.
HIV+ individuals with late latent syphilis or syphilis of unknown duration. Clinical and serologic follow-up after treatment is recommended at more frequent intervals in the setting of HIV.

Rarely, in the setting of severe immunosuppression, cytomegalovirus infection may cause genital ulcers; diagnosis requires biopsy and immunohistochemical staining. Nonhealing ulcers also should be examined via biopsy to exclude a neoplastic process. Aphthous ulcerations similar to those described in the gastrointestinal tract also have been reported in the genital region, usually with advanced immunosuppression.

**Infectious Vaginitis**

The most common types of vaginitis are bacterial vaginosis (BV), yeast infections or candidiasis, and trichomoniasis. Data suggest that not only trichomoniasis, but also BV, increase the risk of HIV transmission—despite the fact that BV is not considered an STI. In fact, there is some evidence that BV also may be a risk factor for perinatal transmission of HIV, which suggests the need to consider treatment in patients who are (or wish to become) pregnant.

Prevalence of both BV and Candida increases in the setting of HIV (Table 2). BV and yeast infections are more tenacious, and BV sometimes more severe, in HIV+ women—particularly those with CD4 counts <200/mm³. Both BV and Candida appear to be associated with immunosuppression, which explains why these problems are more likely to occur in women with lower CD4 counts. One area warranting further research is whether BV and Candida show improvement with the introduction of antiretroviral therapy. Some evidence does suggest that the rate of BV infection decreases with administration of highly active antiretroviral therapy (HAART). However, decreases in rates of candidiasis have not yet been reported with antiretroviral treatment.

Candida albicans represents 85% to 90% of vulvovaginal isolates in the general population of women with yeast infection. The data on non-albicans strains in HIV+ vs HIV- women are conflicting. Isolation of non-albicans strains have been found in as many as 26% to 27% of vaginal cultures in HIV+ women in some studies. Spinillo found a higher frequency of non-albicans species in HIV+ women with recurrent vulvovaginal candidiasis, but other studies have reported no differences in speciation. The most common non-albicans strain found is Torulopsis glabrata. In general, non-albicans strains are less likely to be responsive to conventional antifungal therapies. At this time, azole resistance is rare in vulvovaginal candidiasis, in contrast to oropharyngeal infection.

HIV+ women may receive standard treatment for BV and trichomoniasis. Because Trichomonas is sexually transmitted, partners must be treated, as well. Candida vaginitis is treated with either topical antifungals or oral fluconazole, but topical treatments generally are preferred. Although 1- and 3-day therapies are available, topical therapies may be more effective when given for at least 7 days. True recurrent candidiasis manifesting in 6 or more episodes per year should be treated for longer periods; treatment options are presented in Table 3. In a randomized, double-blind, placebo-controlled trial, weekly administration of fluconazole 200 mg was effective in preventing vaginal candidiasis in HIV-infected women with CD4 cell counts <300/mm³. However, routine primary prophylaxis for vaginal candidiasis is not recommended and many experts also advise against chronic prophylaxis with recurrent infection, unless this is frequent or severe, because of efficacy of acute therapy and concerns about development of fluconazole resistance.

### Table 2. Characteristics of Infectious Vaginitis in HIV-Positive Women

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bacterial Vaginitis</th>
<th>Trichomonas</th>
<th>Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increases in:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV transmission</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Colonization</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistence</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(with CD4 &lt;200 mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Association with</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>immunosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection with HAART</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

**HAART** = highly active antiretroviral therapy.

### Table 3. Treatment for Recurrent Candidiasis in HIV-Positive Women

- Topical therapy for 7-14 days or fluconazole 150 mg po repeated 3 days later, followed by:
  - Fluconazole 100-150 mg po q wk
  - Itraconazole 400 mg q mo or 100 mg po qd
  - Intermittent topical therapy
  - Boric acid suppositories

**po** = by mouth; **q** = every; **qd** = every day.

Data from Abularach S et al.
Because women with HIV often take antibiotics for various forms of infection, yeast infections are a common comorbidity. Clinicians who prescribe antibiotics also should consider advising women to use over-the-counter prophylactic antifungals. In the HIV setting, it is important to avoid empirical treatment of vaginitis as a substitute for clinical examination. Patients should be counseled to avoid douching, which might actually increase risk for vaginitis.31

**Pelvic Inflammatory Disease**

PID appears to be more common in women with HIV; a recent analysis of hysterectomy specimens, matched for surgical indication, found chronic endometritis twice as often in HIV+ women as compared with HIV- women.32 Some studies suggest that the clinical presentation of PID in the setting of HIV also may be more severe or otherwise altered (eg, lower white blood cell counts than seen in HIV- women).13-30

Response to standard parenteral and oral antibiotic regimens in HIV+ women is similar to that seen in women without HIV, and treatment recommendations also remain the same,13 although some experts believe significant immunosuppression is an indication for hospitalization.

**Human Papilloma Virus/ Lower Genital Tract Neoplasia**

HIV+ women are 2 to 3 times more likely than women without HIV to be infected with HPV.30 This includes increased frequency of genital warts,30 as well as other lower genital tract manifestations of HPV. HIV not only increases the likelihood of acquiring HPV, but also increases the persistence of HPV infection.33 In addition, HIV+ women typically have higher HPV viral loads and are more likely to have multiple HPV subtypes.39 A greater prevalence of oncogenic subtypes also is seen in this population. Oncogenic subtypes may be more common with lower CD4 counts and/or higher viral loads, such as with more advanced disease.40,41 Thus, it is not surprising that abnormal cervical cytology (abnormal Pap smears) are approximately 10 times more common among HIV+ women, with both the frequency and severity of the abnormality increasing as CD4 counts decline and viral load increases.42 Progression or regression of dysplasia appears to be associated with the level of immune function and viral load.43,44 Dysplasia in the lower genital tract tends to involve a larger area of the cervix as well as other areas of the lower genital tract, such as the vagina, vulva, and perianal region,45-51 prompting concerns about development of invasive cancer in other areas of the lower genital tract. Table 4 lists recommendations for frequency of Pap smears in HIV+ women.28,30,31

When the Pap smear is abnormal (atypical squamous or glandular cells, or squamous intraepithelial lesion) clinicians should perform a careful colposcopic examination of the cervix49 and the entire lower genital tract, applying a diluted solution (3% to 5%) of acetic acid to highlight abnormalities with biopsy of abnormal areas. Colposcopy also should be considered when there is a history of untreated abnormal Pap smears or evidence of HPV infection. Clinicians also may wish to consider colposcopy in patients with CD4 counts <200/mm3.28 Vulvar lesions suspicious for dysplasia include warts with atypical appearance; raised, often hyperpigmented, lesions; hypopigmented or hyperkeratotic lesions; or nonhealing ulcers. When any of these are present, colposcopy and directed biopsy should be performed.

Anal dysplasia and HPV typically are discussed in the setting of homosexual men, but both are in fact also a concern for HIV+ women. In one study, anal HPV was more prevalent than cervical HPV in HIV+ and high-risk HIV- women.50

The anal canal has a transformation zone similar to the cervix, creating an environment conducive to epithelial changes and vulnerability to neoplastic transformation. Anal Pap sensitivity is similar to that of cervical Pap, but less accurately reflects the grade of the abnormality.51 Although anal Pap smear screening is not yet recommended for routine practice, it should be considered when available, and an abnormal anal Pap should be followed with a referral for high-resolution anoscopy and biopsy.

Treatment for cervical intraepithelial neoplasia (CIN) is indicated for women who have high-grade lesions that are documented on histology or suggested by cytology with discordant findings on histology.48 Treatment options include cervical conization, an outpatient procedure performed under general anesthesia, or loop exci-

### Table 4. Suggested Frequency of Pap Smears for HIV-Positive Women

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Screening Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Pap</td>
<td>2 × in first year, then 1 ×/year</td>
</tr>
<tr>
<td>Symptomatic HIV w/CD4 &lt;200/mm³</td>
<td>6 months</td>
</tr>
<tr>
<td>ASCUS/LSIL evaluated, followed without treatment</td>
<td>4-6 months</td>
</tr>
<tr>
<td>Following treatment of preinvasive lesions</td>
<td>3-4 months for 1 year, then every 6 months</td>
</tr>
</tbody>
</table>

ASCUS = atypical cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion.
Hormonal Contraception

Hormonal methods of contraception include combined oral estrogen-progestin pills, as well as progestin-only methods, such as the 3-month injection. Newer combined estrogen-progestin hormonal methods include a weekly patch and a monthly intravaginal ring. Medroxyprogesterone acetate and estradiol cypionate, a monthly combined hormone injection, currently is not commercially available in the United States. Hormonal contraceptives have some potential disadvantages in the HIV setting, one being that they do not protect against STIs. In addition, some studies show that their use may be associated with increased cervical HIV shedding. There also are conflicting data as to whether or not these methods increase risk of HIV transmission.

Finally, oral contraceptives interact with a number of antiretroviral drugs used by HIV+ patients (Table 5). Oral contraceptives should not be prescribed with either amprenavir or fosamprenavir because they decrease blood levels of these antiretroviral agents when coadministered. Nevertheless, the high contraceptive efficacy and other benefits of combined hormonal contraception, such as decreased anemia, decreased PID, and decreased fibrocystic breast disease, also should be considered, and the disadvantages may be outweighed by the risks of unintended pregnancy.

Intrauterine Devices (IUDs)

Considerable controversy exists surrounding the use of IUDs in the setting of HIV. In an Italian cross-sectional study, women who were steady partners of men with HIV and used IUDs had an increased risk of becoming infected with HIV. In addition, use of

Table 5. Oral Contraceptives and Antiretroviral Therapy: Drug Interactions

<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTV, NFV, LPV</td>
<td>40%-50% decrease in EE levels; use alternative/additional method</td>
</tr>
<tr>
<td>APV</td>
<td>decrease in EE and norethindrone levels; 20% decrease in APV levels: do not coadminister; use alternative method</td>
</tr>
<tr>
<td>ATV</td>
<td>EE increase by 48%, norethindrone increase of 110%; use lowest effective dose or alternative method</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-Nucleoside Reverse Transcriptase Inhibitors</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP</td>
<td>20% decrease in EE levels; use alternative/additional method</td>
</tr>
<tr>
<td>EFV</td>
<td>37% increase in EE levels, clinical significance unknown; use alternative/additional method</td>
</tr>
</tbody>
</table>

RTV = ritonavir; NFV = nelfinavir; LPV = lopinavir; EE = ethinyl estradiol; APV = amprenavir; ATV = atazanavir; NVP = nevirapine; EFV = efavirenz.

Data from Department of Health and Human Services.
IUDs is associated with an increased risk of PID, particularly shortly after insertion. IUDs do not protect against HIV or STIs. However, some studies suggest IUDs are a viable option for HIV+ women. A study by Morrison et al showed no increase in infection-related complications after 24 months of IUD use, and Richardson reported no increase in cervical HIV shedding 4 months after IUD insertion. On the other hand, IUDs that are not progestin releasing are associated with heavier and longer menstrual flow, which may increase the risk of both HIV transmission and anemia. The newer levonorgestrel-releasing IUD, Mirena, has the advantage of reducing menstrual bleeding and flow and is a more appropriate choice if an IUD is considered in the setting of HIV.

**Spermicides**

With frequent use, spermicides have been associated with an increase in mucosal irritation and genital ulcers, potentially increasing the risk of HIV transmission. A recent UNAIDS clinical trial in Africa and Thailand found significantly higher HIV seroconversion rates in nonoxynol-9 users. However, these findings should be interpreted with caution as study subjects were commercial sex workers and so at greater risk than the general population for HIV infection. Despite these disadvantages, spermicides may have a role in contraception in some HIV+ women who are involved in a stable relationship.

**Sterilization, Diaphragm**

Sterilization provides no protection against STIs, but does reduce the risk of PID. Although diaphragm use has not been studied extensively in the HIV setting, we do know that it provides limited STI protection. However, there is no evidence that the diaphragm provides any protection against HIV transmission.

**Emergency Contraception**

This is not a method of routine contraception, but should be considered following an episode of unprotected intercourse or a broken condom. Combined oral contraceptive pills with ethinyl estradiol and norgestrel or levonorgestrel alone reduces the pregnancy rate by at least 74%, if taken within 72 hours. Again, use of oral contraception does not provide STI/HIV protection.

**Condoms**

Use of condoms should be encouraged with all sexual activity, even when other types of contraception are used, in order to prevent transmission of HIV to sexual partners and to prevent acquisition of other STIs. If condoms are used correctly and consistently with every act of intercourse, they are very effective, providing 98% protection against HIV and STI and 95% to 97% protection against pregnancy. Unfortunately, “real-life” use is associated with up to 12% failure rate in prevention of pregnancy and condoms are less likely to be used consistently when more effective methods of contraception are used.

**Conclusion**

Gynecologic disorders are significantly more prevalent in HIV+ women compared with HIV- women. Approaches to management must take into consideration the special needs and risks of this population. Medical evidence surrounding the relationship between HIV transmission/progression and many gynecologic disorders is conflicting, and in many cases, inconclusive. In this setting of uncertainty, clinical caution and careful management are imperative.

**References**

72. Richardson BA. Nonoxynol-9 as a vaginal microbicide for prevention of sexually transmitted infections: it’s time to move on. JAMA. 2002;287:1171-1172.