Gynecologic Problems for HIV Infected Women

Chapter 6:

Gynecologic Problems

Jean R. Anderson, MD
Director, The Johns Hopkins HIV Women's Health Program
Professor, Gynecology and Obstetrics
The Johns Hopkins Medical Institutions

6

Chapter 6: Gynecologic Problems

Chapter 6 at a Glance

6

A Problem-Oriented Approach to Common Gynecologic Complaints

Gynecologic problems are common among HIV infected women and are frequently present at the time of initial presentation for evaluation and care. Minkoff and colleagues found, with prospective assessment over 1 year, that 47% of 262 HIV infected women had at least one incident gynecologic condition (*Am J Obstet Gynecol* 1999;180:824). A study of women admitted to an inpatient AIDS service revealed that although only 9% were admitted with a primary gynecologic problem, 83% had coexisting gynecologic disease when evaluated (*Clin Infect Dis* 1997;25:706). Some gynecologic issues are unrelated to a patient's serologic status, whereas others are directly related to HIV disease and associated immunosuppression. Still others are associated epidemiologically with HIV because of common risk factors such as sexual behavior or substance abuse.

Because HIV infection primarily affects women during their reproductive years, gynecologic and reproductive healthcare play an important role in the overall care of HIV infected women. With improved longevity and quality of life, gynecologic problems may be encountered more commonly or may be more prominent. With these issues in mind, the goal of this chapter is to use a problem-oriented approach in reviewing the most common gynecologic complaints together with their differential diagnosis, evaluation, management, and relationship to HIV.

6

Abnormal Uterine Bleeding and Amenorrhea

What is considered "abnormal" bleeding? A normal menstrual period should occur every 21–35 days and last from 2–6 days. The average blood loss during menses is 20–60 mL, but up to 14% of healthy women have blood loss >80 mL and, as a result, are more likely to be anemic (*Comprehensive Gynecology*. 6th ed. St. Louis: Mosby; 2012). Abnormal bleeding may be of several types, described below along with the most common causes of each type.

- **Menorrhagia:** excessive or prolonged menstrual bleeding, defined as blood loss >80 mL and/or periods lasting for >7 days. Menorrhagia is most commonly caused by fibroids or by a hemostatic disorder.

- **Metrorrhagia:** light bleeding from the uterus at irregular intervals, often caused by hormonal contraception or continuous hormone replacement therapy (HRT) in the first few months after initiation. Megestrol can cause metrorrhagia. Pregnancy should be ruled out.

- **Menometrorrhagia:** heavy bleeding from the uterus at irregular intervals, commonly caused by anovulation, fibroids, or uterine or cervical neoplasm

- **Intermenstrual bleeding:** bleeding that occurs between menses or during expected times of hormonal withdrawal in women using hormonal contraception. Intermenstrual bleeding is commonly caused by polyp(s) or is breakthrough bleeding with hormonal contraception.

- **Oligomenorrhea:** bleeding that occurs at intervals >35 days. Oligomenorrhea is generally caused by ovulatory dysfunction, but may be normal with newer extended-phase oral contraceptives.

- **Polymenorrhea:** bleeding that occurs at intervals <24 days. It may indicate ovulatory dysfunction.

- **Postcoital bleeding:** vaginal bleeding noted within 24 hours of vaginal intercourse when not at the expected time of menses. This type of bleeding may indicate cervicitis. Cervical neoplasm must be ruled out.

- **Postmenopausal bleeding:** any vaginal bleeding or spotting after total cessation of menses. If a woman is on HRT, this is any bleeding that occurs at times other than expected withdrawal. Neoplasm must be ruled out.

- **Dysfunctional uterine bleeding:** excessive, noncyclic uterine bleeding that is not caused by an anatomic lesion or systemic disease. Most often, it is caused by anovulation.

- **Amenorrhea:** absence of menstrual bleeding. Primary amenorrhea is the absence of menses by age 16. Secondary amenorrhea is the absence of menses for a variable period of time—at least 3 months, but generally 6 months or longer—in a woman who has previously menstruated.

Relationship to HIV disease: Menstrual disorders are reported by 20%– 30% of HIV infected women (*J Obstet Gynaecol Res* 2010;36(5):1053; *J Womens Health* 2006;15(5):591; *AIDS Patient Care STDS* 2009;23(6):463). Older controlled studies yielded conflicting evidence regarding a clinically significant direct effect of HIV or HIV-related immunosuppression on menstrual function (*J Acquir Immune Defic Syndr Hum Retrovirol* 1996;12:489; *Obstet Gynecol* 1996;87:1030; *Obstet Gynecol* 1994;83:397). Several more recent large cross-sectional and cohort studies, however, suggest that, when compared with uninfected women, HIV infected women are more likely to have amenorrhea, oligomenorrhea, and irregular periods (*J Obstet Gynaecol Res* 2010;36(5):1053; *Obstet Gynecol* 2006;108(6):1423; *Obstet Gynecol* 2006;108(6):1423) and/or that menstrual abnormalities may be more common with lower CD4+ cell counts (*J Obstet Gynaecol Res* 2010;36(5):1053; *J Acquir Immune Defic Syndr* 2000;24:68; *J Womens Health* 2006;15(5):591).

Some studies also suggest that taking antiretroviral therapy (ART) and/or having suppressed HIV RNA levels may reduce the prevalence or incidence of menstrual disorders (*J Obstet Gynaecol Res* 2010;36(5):1053; *J Womens Health* 2006;15(5):591; *AIDS Patient Care STDS* 2009;23(6):463). Analysis of data collected at 6-month intervals from women in the WIHS prospective cohort indicated no difference in the prevalence or incidence of menstrual disorders by HIV serostatus; amenorrhea and oligomenorrhea were less likely, however, in women with CD4+ cell counts >200 cells/mm^3. Both effective ART and higher CD4+ cell counts were associated with lower rates of incident menstrual abnormalities (*J Womens Health* 2006;15(5):591). In a recent cross-sectional study from Spain, approximately 75% of HIV infected women with menstrual disorders attributed the disorders to the use of ART; two-thirds of those women were <95% adherent to their antiretroviral (ARV) regimens (*AIDS Patient Care STDS* 2009;23(6):463).

Most studies of menstrual function in HIV infected women have relied on patient self-report of menstrual function; accurate determination of the cause of abnormal function, however, requires hormonal levels and potentially endometrial biopsy. In a study of HIV infected women with prolonged amenorrhea (>1 year), follicle-stimulating hormone (FSH) levels were assessed and levels >25 mIU/mL were used to define the presence of ovarian failure. More than 50% of the HIV infected women with prolonged amenorrhea, including 75% of women aged ≥45, did not have ovarian failure. After adjusting for age, HIV infected women were about threefold more likely than uninfected women to have prolonged amenorrhea without ovarian failure (*Obstet Gynecol* 2006;108(6):1423). Independent predictors of prolonged amenorrhea without ovarian failure included opiate use, low serum albumin (reflecting poor nutritional status or liver disease), and a history of AIDS-defining illness. These findings highlight the fact that amenorrhea may be incorrectly interpreted as menopause, with significant implications for patients who discontinue contraception on the basis of that presumption.

Some of the variability in previous study results may represent failure to take into account potential confounding variables. In the setting of HIV infection, those variables include age, weight loss, body mass index (BMI), chronic disease or opportunistic infections (including hepatitis), drug and alcohol abuse (*Menopause* 2007;14(5):859; *Obstet Gynecol* 2006;108(6):1423), and use of psychotherapeutic medications (*Am J Obstet Gynecol* 2003;188:881). Progestational agents used for appetite stimulation or contraception also may be related to menstrual dysfunction. Menorrhagia, or excessive menstrual blood loss, has been reported with ritonavir (*Lancet* 1999;353:811) and more recently with atazanavir (*Int J STD AIDS* 2007;18(9):651).

6

History, Physical Exam, Evaluation, Differential Diagnosis, and Management of Abnormal Bleeding

History

- **Characteristics of bleeding:**
  - Date of last normal menstrual period
  - Duration and frequency of menses
  - Amount of bleeding (i.e., number of pads/tampons used per day)
  - Presence of clots or associated pain/cramping
  - Duration and pattern of menstrual irregularities or amenorrhea
  - Presence of intermenstrual or postcoital bleeding
- **History of other abnormal bleeding:**
  - Gastrointestinal bleeding or bleeding from the urinary tract (vs. from a gynecologic source)
  - Easy bruising
  - Nose or gum bleed
- **History of gynecologic problems and/or other symptoms:**
  - Abnormal Pap smears
  - Uterine fibroids or polyps
  - Prior ectopic pregnancy
  - Abnormal vaginal discharge

- **Medical history:**
  - Timing of diagnosis of HIV/AIDS
  - Comorbid conditions, including hepatitis
  - Clinical symptoms of HIV
  - CD4+ cell count and viral load (VL)
  - Platelet disorders; thrombocytopenia is frequently diagnosed in patients with HIV infection, particularly those with more advanced stages of disease (*Eur J Haematol* 1992;48:168)
  - Substance abuse
  - Medications
- Sexual history: Last sexual intercourse and use of contraception and condoms

Physical Exam

- **Abdominal exam:** Presence of abdominal tenderness or mass
- **External genitalia, vagina, and cervix:** Inflammation and actively bleeding lesions (e.g., lacerations, condylomata, polyps)
- **Bimanual and rectovaginal exam:**
  - Pelvic tenderness
  - Enlarged uterus
  - Other pelvic mass

Evaluation

Further evaluation or referral is indicated based on results of the tests outlined below, severity of the problem, and response to basic management.

- **Pregnancy test** (urine or serum): All women within reproductive age range
- **Blood tests:**
  - Complete blood count (CBC)
  - Platelet count
  - Coagulation profile: with evidence of systemic bleeding, rule out coagulopathy
  - Thyroid-stimulating hormone (TSH), prolactin levels: consider with any irregular bleeding/amenorrhea without apparent cause
  - FSH, estradiol: with oligomenorrhea/amenorrhea and/or signs/symptoms of decreased estrogen production (hot flashes, vaginal atrophic changes); particularly helpful in distinguishing ovarian failure (low estradiol, high FSH) from hypothalamic amenorrhea, as with wasting (low estradiol, low/normal FSH)
- **Cervical testing:** Gonorrhea, chlamydia
- **Pelvic ultrasound:**
  - With finding of uterine enlargement, adnexal mass, significant tenderness, or positive pregnancy test
  - Transvaginal approach commonly used in evaluation of abnormal bleeding to assess endometrial thickness, especially in peri- and postmenopausal women or to look for other possible abnormalities (e.g., polyps, fibroids)
- **Endometrial biopsy:**
  - Postmenopausal bleeding
  - Prolonged amenorrhea followed by onset of irregular or heavy bleeding
  - Persistently irregular bleeding
  - Used liberally with any form of abnormal bleeding if no other cause is found and bleeding does not respond to conservative management with progestins or oral contraceptives
  - Helpful in diagnosing endometritis, endometrial hyperplasia, and uterine cancer
  - Necessary for diagnosis of cytomegalovirus (CMV) or tuberculous endometritis; alert pathologist if these are considerations

• **Pap smear:**
  - May be inadequate with active bleeding
  - Biopsy required if cervical lesion is seen

Differential Diagnosis

• **Pregnancy:**
  - Must be considered in any woman of reproductive age with irregular bleeding or amenorrhea
  - May be intrauterine or ectopic (usually tubal)
  - Bleeding with intrauterine pregnancy may indicate threatened or incomplete abortion or miscarriage
  - If later in pregnancy, may indicate serious obstetric complication

• **Anovulation:**
  - Most common cause of abnormal uterine bleeding among women of reproductive age. Women with anovulation typically have a history of menstrual irregularity.
  - Onset of heavy and prolonged bleeding may follow several months of no bleeding. Anovulatory bleeding is a diagnosis of exclusion; organic, systemic, and iatrogenic causes must be ruled out.
  - More common among perimenopausal women and adolescents soon after menarche, along with oligo-ovulation

• **Perimenopause/menopause:** Declining estrogen levels may cause irregular menses; menopause is associated with cessation of menses

• **Uterine fibroids:** Common benign uterine tumors; usually asymptomatic, but may cause heavy and/or prolonged periods

• **Adenomyosis:**
  - Migration of endometrial glands and stroma into uterine muscle (myometrium)
  - Uterus often somewhat enlarged and boggy to palpation
  - Benign condition

• **Cancer:**
  - Malignant processes in vulva, vagina, cervix, uterus, fallopian tubes, and ovaries may present with abnormal bleeding
  - Most common in postmenopausal women
  - Non-Hodgkin's lymphoma of endometrium has been reported in the setting of HIV (*Obstet Gynecol* 1997;90(4 Pt 2):697)

• **Genital tract infections:**
  - Cervicitis, endometritis, vaginitis, and vulvitis may present with abnormal vaginal bleeding or spotting
  - Aids to diagnosis include pain and/or tenderness, discharge, fever, and other signs and symptoms of infection
  - In the setting of severe immunosuppression, consider opportunistic processes, including tuberculous or CMV endometritis

• **Medical conditions:**
  - Thyroid disorders: hypothyroidism or hyperthyroidism
  - Coagulopathy, including platelet disorders
  - Cirrhosis
  - Chronic illness
  - Wasting

• **Substance abuse:** Drug use, including methadone, can lead to disturbances of the hypothalamic-pituitary axis, with resulting irregular bleeding or amenorrhea

• **Medications:** Hormonal agents: Progestational agents, such as those used for contraception (e.g., depot medroxyprogesterone acetate [DMPA], etonogestrel implant) or for appetite stimulation (e.g., megestrol acetate), frequently cause irregular vaginal bleeding. Combined estrogen-progestin contraceptive methods generally result in regular menstrual periods, although some breakthrough bleeding may occur early after initiation; inconsistent use can cause bleeding and increase

6

risk for pregnancy. Consider antiretroviral agents as a potential cause of abnormal bleeding. Medications that can affect prolactin concentrations and possibly result in amenorrhea include psychotropic drugs (tricyclic antidepressants, phenothiazines, opiates) and metoclopramide. Thalidomide has also been associated with the development of secondary amenorrhea (*Eur J Dermatol* 2002;12:63).

Management of Abnormal Bleeding

Management depends on the diagnosis and on the results of testing.

- **Positive pregnancy test:** Refer to specialist. If suspect ectopic pregnancy (based on pain, HCG levels and ultrasound findings) requires urgent evaluation and treatment.
- **Suspected anovulatory bleeding:** Medical management with oral contraceptive pills or cyclic progestins: DMPA 10 mg po qd for 10–14 days each month
  - May restore regular menstruation, reduce the possibility of anemia, and protect endometrium from prolonged estrogenic stimulation, which can cause hyperplasia or neoplasia
  - Oral contraceptives also provide effective contraception but are contraindicated in heavy smokers aged >35 years and with hypertension or other cardiovascular disease, diabetes, or markedly abnormal liver function
- **Refer to specialist for:**
  - Severe bleeding and anemia
  - Pelvic mass
  - Suspected malignancy
  - Bleeding not resolved with conservative measures

Abnormal Pap Smear

In the setting of HIV infection 30%–60% of Pap smears exhibit cytologic abnormalities and 15%–40% have evidence of dysplasia; these rates are 10–11 times greater than those observed among women who are not HIV infected (*J Natl Cancer Inst Monogr* 1998;23:43).

HIV and Human Papillomavirus

The spectrum of human papillomavirus (HPV) disease includes subclinical disease, classic genital warts and other HPV-related skin lesions, lower anogenital-tract intraepithelial neoplasia, and invasive cancers of the lower genital tract and anal canal. There are >100 HPV subtypes, categorized as low, intermediate, or high risk on the basis of their oncogenic potential, though the categories are not exclusive; low-risk HPV types have been described in cervical carcinomas.

HPV is an extremely common infection. Studies suggest that more than 50% of sexually active adults have been infected with one or more genital HPV types, but most HPV infections are transient (*J Infect Dis* 1995;171:1026; *N Engl J Med* 1998;338:423). HPV VL is independently associated with HPV persistence (*J Infect Dis* 2001;184:682).

Compared with women who are not HIV infected, women with HIV have

- higher prevalence and incidence of HPV (*Int J STD AIDS* 2003;14:417; *J Infect Dis* 2001;184:682),

- higher HPV VL (*Am J Obstet Gynecol* 2002;186:21),

- longer persistence of HPV infection (*Am J Epidemiol* 2000;151:1148; *N Engl J Med* 1997;337(19):1343),

- a higher likelihood of infection with multiple HPV subtypes (*Am J Obstet Gynecol* 2002;186:21; *Acta Cytol* 2009;53:10, *Br J Cancer* 2007;96(9):1480; *Arch Virol* 2007;152:75), and

- greater prevalence of oncogenic subtypes (*Am J Obstet Gynecol* 1998;178(5):982; *J Med Virol* 1998;56:133; *Acta Cytol* 2009;53:10).

Among HIV infected women with normal cervical cytology, the rate of cervical HPV infection has been found to vary from >30% in Asia, North America, and Europe to >55% in South America, Central America, and Africa (*AIDS* 2006;20:2337).

In HIV infected women the prevalence and persistence of HPV infection increase as CD4+ cell counts decrease and HIV VL increases (*J Natl Cancer Inst* 1999;91:226; *Obstet Gynecol* 2008;111:1380). Higher HPV VLs are also associated with lower CD4+ cell counts (*Obstet Gynecol* 2000;96(3):403). Some studies have found that oncogenic HPV types may be more common with lower CD4+ cell counts and/or higher HIV VL (*J Infect Dis* 1999;179:1405; *Am J Obstet Gynecol* 1998;178(5):982; *Br J Cancer* 2007;96:1480). Immunosuppression also may increase the risk of clinically expressed (versus latent) HPV infection by approximately twofold in HIV infected women with CD4+ cell counts >500 cells/mm^3 to as much as 10-fold in women with CD4+ cell counts <200 cells/mm^3 (*Obstet Gynecol* 1995;85(5 Pt 1):680).

HIV and cervical dysplasia: Both the prevalence and incidence of abnormal Pap smears are greater among HIV infected women than among uninfected women. Abnormal cervical cytology is associated with the presence of HPV infection and the degree of immunosuppression. The frequency and severity of abnormal Pap smears, as well as histologically documented dysplasia, increase with declining CD4+ cell counts and have also been associated with higher HIV RNA levels (*Gynecol Obstet Invest* 1995;40:52; *Gynecol Oncol* 2001;80(3):350; *JAMA* 2000;282:1031; *AIDS Care* 2007;19:1052; *Obstet Gynecol* 2008;111:1388; *J Acquir Immune Defic Syndr* 2001;27:432). Increased HPV VL, seen in women with more-advanced HIV, is associated with increased frequency, severity, and incidence of cervical dysplasia (*Obstet Gynecol* 2000;96(3):403; *J Clin Microbiol* 2003;41:2763; *Am J Obstet Gynecol* 2001;184:322). HIV is also associated with more extensive and/or a larger volume of cervical involvement (*Gynecol Oncol* 1990;38:377).

Progression and regression of Pap smear abnormalities have been associated with level of immunosuppression and plasma viremia, as reflected in the CD4+ cell count and HIV VL (*J Acquir Immune Defic Syndr* 2001;27:432; *J Infect Dis* 2003;188(1):128). The incidence of invasive cervical cancer, however, is not higher among HIV infected women who are screened regularly and receive recommended treatment than among women who are not HIV infected (*Obstet Gynecol* 2004;104:1077; *Cancer* 2009;115:524).

Invasive cervical cancer in HIV disease: In 1993, the U.S. Centers for Disease Control and Prevention (CDC) expanded the case definition of AIDS to include invasive cervical cancer (ICC). Oncogenic HPV types play a central role in the relationship between HIV and cervical cancer. Recent data from Africa indicate that in the absence of high-risk HPV, there was no increased risk for cervical cancer among HIV infected women (*J Infect Dis* 2003;188:555). In a study of ICC in both HIV infected and uninfected Kenyan women, HPV types 16 and 18 were the most common and were detected in 65% of ICCs in the HIV infected patients, with potential implications for prevention with HPV vaccines. Almost half of the cancers associated with HPV type 16 or 18 involved multiple HPV types (*Int J Cancer* 2008;122:244).

Analysis of matching data from AIDS and cancer registries in 15 regions in the United States indicates an increased risk of ICC among women with AIDS relative to HIV uninfected women (*J Natl Cancer Inst* 2009;101(16):1120); however, among women diagnosed with AIDS between 1996 (when ARVs were introduced) and 2004, ICC was not significantly increased in women with low CD4+ cell counts, a finding that may reflect the effects of active screening (*Natl Cancer Inst* 2009;101(16):1120). Other studies have found no evidence of an increased incidence of ICC among women who are screened regularly and who receive appropriate evaluation and treatment of abnormal Pap smears (*Obstet Gynecol* 2004;104:1077; *Cancer* 2009;115:524).

Cervical cancer affects HIV infected women at younger ages than it does uninfected women (about a decade earlier). Compared with other opportunistic infections (OIs), cervical cancer affects HIV infected women with more intact immune systems (*Gynecol Oncol* 2000;77:460).

HIV infected women with ICC may present at more advanced stages (especially with CD4+ cell counts <200 cells/mm^3). ICC may also behave differently in HIV infected women: it may metastasize to unusual locations (e.g., psoas muscle, clitoris, meninges), respond more poorly to standard therapy, recur more frequently and at shorter intervals, cause death more often, or progress to death more rapidly than it does in uninfected women with ICC at a similar stage (*Obstet Gynecol* 1996;88:269; *Gynecol Oncol* 1990;38:377).

HIV- and HPV-related dysplasia outside of the cervix: The association of HPV with disease outside of the cervix is also linked to persistent infection with oncogenic HPV subtypes and to the level of immunosuppression.

Compared with high-risk uninfected women, HIV infected women have about a 10-fold increase in the prevalence and incidence of vulvar (VIN), vaginal (VAIN), and perianal (PAIN) dysplasia or intraepithelial neoplasia (*Obstet Gynecol* 2006;107:1023; *AIDS* 1996;10:1641; *Gynecol Oncol* 1995;61:384; *Gynecol Oncol* 1990;38:377; *Gynecol Oncol* 1996;60:30; *Obstet Gynecol* 1994;83:205). In the WIHS cohort, VIN incidence was greater among HIV infected women and was associated with abnormal Pap smears and high- or medium-risk HPV. ART was associated with reduced VIN (*Am J Obstet Gynecol* 2004;190:1241).

Genital warts:

Anal HPV and/or dysplasia: Anal HPV has been reported in up to 90% of HIV infected women and is more common with lower CD4+ cell counts and in the presence of cervical HPV and/or cervical dysplasia (*Eur J Obstet Gynecol Reprod Biol* 2008;140(1):103; *J Infect Dis* 2001;183:383; *Sex Transm Dis* 2011;38(4):253). Multiple HPV types and oncogenic types are common (*Sex Transm Infect* 1999;75:172).

Abnormal anal cytology or anal squamous intraepithelial lesions (ASIL) have been reported in up to 26% of HIV infected women. Risk factors include a lower CD4+ cell count, increased HIV VL, high HPV VL, history of receptive anal intercourse, and concurrent abnormal cervical cytology (*J Natl Cancer Inst* 2001;93:843; *AIDS* 1993;7:43). Even with the use of ART, high-grade anal intraepithelial neoplasia was found in 9% of HIV infected women in a large prospective study (*AIDS* 2009;23:59).

The sensitivity of anal Pap smears appears to be similar to that of cervical cytology, although the grade of anal dysplasia may not correlate well with histology (*Int J STD AIDS* 2007;18:77).

6

The incidence of invasive anal cancer is seven- to 20-fold greater among women with HIV/AIDS than among women in the general population, with the highest incidence observed among women with AIDS (*J Natl Cancer Inst* 2000;92(18):1500; *J Natl Cancer Inst* 2009;101(16):1120).

Oral disease: Oral HPV infection is more common among HIV infected than uninfected women, although both the prevalence and incidence of oral HPV infection are substantially lower than cervical HPV infection (*Int J Cancer* 2007;121:143). A meta-analysis of cancer incidence in HIV infected patients indicated that cancers of the oral cavity or pharynx are 2.32 times as likely to develop in patients with HIV infection as in uninfected patients (*Lancet* 2007;370:59).

Effect of Antiretroviral Therapy on Human Papillomavirus–related Disease

Conflicting findings: The role of ART and immune reconstitution in reducing the incidence and progression of and promoting the regression of HPV infection and cervical or other abnormalities remains unclear. Conflicting findings may be related to any of a number of factors: differences in study design, screening and diagnostic protocols, virologic and immunologic parameters, duration and type of ART, length of follow-up, recruitment and referral strategies, and definitions of screening test and disease positivity.

In some studies, ART has been associated with increased regression and decreased risk of progression of cervical cytologic abnormalities and with increased regression of cervical dysplasia (*AIDS* 2002;16:1799; *AIDS* 2001;15:2157). Among women with pre-existing abnormal cervical cytology in the HERS cohort, ART was associated with enhanced HPV clearance but not with regression of abnormal Pap results (*Obstet Gynecol* 2009;113(1):26). In a study of women initiating ART, a high prevalence of cervical HPV DNA found at baseline declined over 8 months of ART (*J Acquir Immune Defic Syndr*

2009;51(3):274). In another study, with 15 months of follow-up, persistence of high-risk HPV and progression of squamous intraepithelial lesions (SIL) were comparable among three groups: women not on ART, women treated with nucleoside analogues only, and women on effective ART (*J Infect Dis* 2001;184:547).

In a more recent analysis from WIHS, the prevalence, incidence, and clearance of HPV infection and/or SILs were compared among women before and after they initiated ART. Use of effective ART and good adherence (≥95% of medications taken) were associated with a significant reduction in the prevalence and incident detection of oncogenic HPV infection and with decreased prevalence and more-rapid clearance of oncogenic HPV-positive SILs (*J Infect Dis* 2010;201(5):681). Six months of ART had no effect on anal HPV or ASIL (*J Acquir Immune Defic Syndr* 2001;28(5):422). Another analysis indicated that anal cancer was the only cancer found to be increasing in incidence among HIV infected people in the United States in the ART era (*Ann Intern Med* 2008;148(10):728). The incidence of high-grade vulvar neoplasia was not reduced with ART use (*Am J Obstet Gynecol* 2004;190:1241), even though rates of low-grade vulvar lesions and anal or genital warts did decrease with ART (*Am J Obstet Gynecol* 2004;190:1241).

Why don't HPV-related lesions respond to ART as other opportunistic illnesses do? Although there is partial restoration of immune competence with ART, this may be counteracted by increasing longevity, with increased cumulative exposure to oncogenic HPV infections and the accumulation of somatic mutations and epigenetic changes that contribute to cervical carcinogenesis. It is likely that women with higher nadir CD4+ cell counts and/or earlier intraepithelial lesions may respond best to effective ART (*J Transl Med* 2009;7:108). HIV infected women should continue to be followed closely for evidence of neoplasia in the lower genital tract, regardless of ART or VL.

Screening Tests

Cervical cytology: Cervical cytology screening programs have been associated with marked reductions in cervical cancer incidence (*Prev Med* 1986;15:582; *Ann Intern Med* 1990;113:214). It is estimated that 60% of women diagnosed with ICC have never had cervical cytology testing or have not been screened within the 5 years prior to diagnosis (NIH Consensus Statement Online 1996;43(1):1; http://consensus.nih.gov/1996/1996CervicalCancer102html.htm. Accessed 7/12/12). Because of errors in sampling or interpretation, false-negative Pap smears are associated with 30% of new cases of cervical cancer each year (NIH Consensus Statement Online 1996;43(1):1; *CA Cancer J Clin* 1995;45:305). A single Pap smear is associated with false-negative rates of 10%–25%; accuracy is significantly improved with regular periodic screening.

The accuracy of standard cervical cytology appears to be similar in both HIV infected and uninfected women (*Obstet Gynecol* 1993;81:372; *Gynecol Oncol* 1998;69:109). In the HERS cohort, HIV infected women were more likely than high-risk HIV uninfected women to have abnormal biopsy results with normal

Pap smears. Most of the HIV infected women, however, developed abnormal Paps within 1 year of the abnormal biopsy results, suggesting that current Pap smear screening guidelines are appropriate (*Clin Infect Dis* 2006;42(4):562).

If available, liquid-based Pap smears are preferred because they appear to decrease the number of inadequate smears and to reduce, but not eliminate, false-negative results; they also offer the possibility of direct HPV testing on collected specimens. Liquid-based Paps, however, are more expensive than conventional Pap tests. A review of more than 400 conventional and liquid-based cytologic screening tests in HIV infected women found that liquid-based preparations reduced the proportion of smears diagnosed as atypical squamous cells of undetermined significance (ASCUS)/atypical glandular cells of undetermined significance (AGCUS) (*Acta Cytol* 2004;48(2):165). It is believed that liquid-based cytology helped to resolve findings of "undetermined significance" into either normal or clearly abnormal results, potentially reducing the need for further evaluation.

6

HPV testing: HPV testing can identify both oncogenic and nononcogenic viral types. In HIV uninfected women, HPV testing for cancer-associated types is used as a triage test to stratify risk in women with a cytology diagnosis of ASCUS, in postmenopausal women with a cytology diagnosis of low-grade squamous intraepithelial lesion (LSIL), and as an adjunct to cytology for primary screening in women aged >30 years (ACOG Practice Bulletin 109; *Obstet Gynecol* 2009;114(6):1409).

The role of HPV DNA testing in HIV infected women, however, is unclear. In a WIHS substudy of HIV infected and uninfected women with normal baseline cytology, incidence of SIL was examined by baseline HPV DNA results and stratified by CD4+ cell count. Over 3 years of follow-up, incidence of any SIL was similar in both HIV uninfected women and HIV infected women with CD4+ cell counts >500 cells/mm^3 who had negative results for oncogenic HPV or all HPV, suggesting that similar cervical cancer screening practices may be applicable to both groups. On the other hand, after just 2 years of follow-up, incidence of any SIL in HIV infected women with CD4+ cell counts <500 cells/mm^3 was increased, even among women with negative results for any HPV, suggesting that a closer screening strategy may be needed for women with lower CD4+ cell counts (*JAMA* 2005;293(12):1471).

The 2006 American Society for Colposcopy and Cervical Pathology (ASCCP) Consensus Guidelines endorse the option of reflex high-risk HPV testing for triage of ASCUS on Pap smear irrespective of HIV status (*Am J Obstet Gynecol* 2007;197(4):346). CDC guidelines, however, although based on limited and conflicting data, recommend routine colposcopy or repeat cytology in 6–12 months for HIV infected women with ASCUS and colposcopy for a higher-grade abnormality (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013). In two prospective studies of HIV infected women with ASCUS, approximately 30% of participants had evidence of oncogenic HPV, a finding that would support the use of HPV testing in this population if HPV testing remained highly sensitive (*J Womens Health* 2004;13:147; *J Low Genit Tract Dis* 2004;8:298). One of these studies,

however, reported a sensitivity of HPV testing of 100% for the detection of cervical intraepithelial neoplasia (CIN) 2 or higher (*J Low Genit Tract Dis* 2004;8:298); the other study reported a sensitivity of only 50% for detecting high-grade CIN (*J Womens Health* 2004;13:147).

Currently, CDC and the American Congress of Obstetricians and Gynecologists (ACOG) do not recommend HPV testing for triage of HIV infected women with abnormal cytology results, for follow-up after treatment for CIN, or to lengthen screening intervals (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo. nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013); ACOG Practice Bulletin 117; *Obstet Gynecol* 2010;116(6):1492).

A study examining HPV DNA testing as a primary screening method for cervical dysplasia in 94 HIV infected women found that HPV DNA testing identified high-grade cervical dysplasia more accurately than Pap smear (*Gynecol Oncol* 1999;75(3):427). Further study is needed regarding a potential role for HPV DNA testing for primary screening in the setting of HIV, especially given the high rates of HPV infection in HIV infected women.

Recommendations for cytologic and other screening and colposcopy:
Pap smear results are reported according to the Bethesda System (*JAMA* 2002;287(16):2114), outlined in Table 6-1.

Table 6-1	
Pap Smear Results: Bethesda System	
Specimen adequacy	• Satisfactory for evaluation: note presence/absence of endocervical transformation zone component • Unsatisfactory for evaluation: specify reason
General categorization	• Negative for intraepithelial lesion or malignancy • Epithelial cell abnormality • Other

Interpretation and/or result	• Negative for intraepithelial lesion or malignancy
	  - Infections
	  - Reactive changes (inflammation, radiation)
	  - Atrophy
	
	• Epithelial cell abnormalities
	  - ASC
	  - ASCUS
	  - ASC-H
	  - LSIL, including HPV changes and mild dysplasia, CIN 1
	  - HSIL, including moderate and severe dysplasia, CIN 2, CIN 3
	  - Squamous cell carcinoma
	  - Glandular cell abnormalities
	
	• Other
	  - Endometrial cells in a woman aged ≥40 years

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Suggested frequency of Pap smears:

- Normal Pap: once yearly
- ASC/LSIL, evaluated and followed without treatment: every 6 months
- Following treatment of preinvasive lesions: every 3–4 months for first year, then every 6 months

Evaluation of abnormal results: Women with HIV infection should be screened with cervical cytology twice in the first year after diagnosis of HIV and, if results are normal, annually thereafter (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013); ACOG Practice Bulletin 109; *Obstet Gynecol* 2009;114:1409). More-frequent Pap smears should be considered with an abnormal Pap smear that is followed conservatively (after colposcopic evaluation to rule out HSIL), with HPV infection, and after treatment for cervical dysplasia.

Although adolescents with HIV have a higher incidence of cervical dysplasia than uninfected adolescents, the incidence of high-grade abnormalities appears to be low (*J Low Genit Tract Dis* 2008;12:199; *J Infect Dis* 2004;190:1413; *Am J Obstet Gynecol* 2009;200:149.e1). Cytologic surveillance in adolescents with HIV should be the same as that recommended for adults.

Pap smear results are reported according to the Bethesda System (see Table 6-1). Abnormal Pap smears (ASCUS or worse) require further evaluation with colposcopy and biopsy of abnormal areas for histologic confirmation and to confirm or exclude a high-grade cervical lesion. The 2006 ASCCP Consensus Guidelines recommend that ASCUS on Pap trigger the use of reflex high-risk HPV testing for triage to colposcopy (HPV positive) vs. short-term cytologic follow-up (HPV negative) for both HIV infected and uninfected women (*Am J Obstet Gynecol* 2007;197(4):346). Current CDC guidelines recommend colposcopy or repeat cytology in 6–12 months for all HIV infected women with ASCUS (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013), irrespective of CD4+ cell count, HIV VL, or ART. Currently, ACOG states that HIV infected women with ASCUS may be monitored with repeat cytology alone or referred for colposcopy (ACOG Practice Bulletin 117; *Obstet Gynecol* 2010;116(6):1492).

Indications for colposcopy of the cervix include

- cytologic abnormality: atypia or greater, including ASC and atypical glandular cells (AGC);
- history of untreated abnormal Pap smear;
- repeat colposcopy in women with AGC not otherwise specified (AGC-NOS) if the initial evaluation is negative and follow-up cytology is abnormal; and
- evidence of HPV infection (consider).

Consider periodic colposcopy

- after treatment of cervical dysplasia, particularly with recurrence or persistence of cytologic abnormalities;

- with ASCUS or LSIL after ruling out a high-grade lesion; and
- with cytologic progression of ASCUS or LSIL that is being followed conservatively.

The finding of ASC represents the mildest Pap smear abnormality. ASC is stratified into two categories: ASCUS and ASC-H. In the general population, 5%–17% of women with ASC have underlying CIN 2–3 and approximately 0.1% have invasive cancer (*J Natl Cancer Inst* 2001;93:293), whereas 24%–92% of women with ASC-H have CIN 2–3 confirmed with biopsy (*JAMA* 2002;287(16):2120). HIV infected women with ASCUS are approximately twice as likely to have underlying dysplasia as are uninfected women (*Obstet Gynecol* 1996;87:515). Immunosuppression does not appear to increase the frequency of dysplasia associated with ASCUS on Pap (*Gynecol Oncol* 1999;75(1):118).

It remains unclear whether HIV infected women with mild cytologic abnormalities are at a similar or increased risk for clinically significant disease (i.e., HSIL or worse) compared with uninfected women. In a cross-sectional study of HIV infected and uninfected women with ASCUS and LSIL, HIV infected women were no more likely to have CIN 2 or higher on biopsy than were uninfected women (*Obstet Gynecol* 2008;112:238). Other studies have shown that with ASCUS or LSIL on Pap and no histologic evidence of high-grade CIN, the absolute risk of progression to CIN 2 or higher is approximately 12% (*Obstet Gynecol* 2005;106(3):525) and that CIN 1 infrequently progresses to more advanced disease (*AIDS* 2004;18:109).

The risk of underlying pathology with a diagnosis of AGC is significant. The 2001 Bethesda System stratifies AGC into three categories: AGC, either endocervical, endometrial, or NOS; AGC, favor neoplasia; and endocervical adenocarcinoma in situ (AIS). Various studies have found that 9%–54% of women with AGC have CIN on biopsy, 0%–8% have AIS on biopsy, and up to 9% have invasive cancer (*JAMA* 2002;287(16):2120). The risk of a significant abnormality increases with the severity of the AGC reading. Colposcopy, as well as endocervical sampling, is indicated with any AGC on Pap. Endometrial sampling is indicated in women aged >35 years and in younger women with AGC who have unexplained vaginal bleeding (*JAMA* 2002;287(16):2120). Women who have AGC, favor neoplasia, or endocervical AIS should undergo a diagnostic excisional procedure (e.g., cervical conization) if the initial evaluation is negative for invasive cancer (*JAMA* 2002;287(16):2120).

Even in high-resource areas, screening for cervical dysplasia in the setting of HIV can be challenging. Women receiving gynecologic and primary HIV care at the same location are more likely to have had Pap-smear screening within the previous year (*J Acquir Immune Defic Syndr* 2001;27:463); however, despite high rates of HPV and CIN, many women with HIV do not engage in the recommended annual Pap testing (*J Womens Health* 2008;17(10):1609; *J Acquir Immune Defic Syndr* 2009;51(4):430).

Vaginal and vulvar screening: Careful visual inspection of the vagina and vulva should be performed at least annually; look for evidence of HPV infection (e.g., warts, hyperpigmented or hyperkeratotic lesions). Consider

vaginal cytology and careful examination and/or colposcopy of the entire lower genital tract (vagina, vulva, and perianal region) with any of the following: visible evidence of cervical, vaginal, or vulvar HPV infection; current CIN or history of CIN; or cervical, vaginal, or vulvar cancer.

Continued vaginal cytologic surveillance is warranted in HIV infected women who have a history of CIN 2 or greater who undergo hysterectomy (ACOG Practice Bulletin 117; *Obstet Gynecol* 2010;116(6):1492). Abnormal vaginal cytology should be evaluated with colposcopy +/– Lugol's iodine, with biopsy of abnormal areas. Persistent ulcer or mass of concern for possible cancer should be biopsied.

Anal screening: Question patients at least annually about such symptoms as rectal bleeding and/or pain and perform an annual digital rectal exam to detect mass on palpation.

The role of anal cytology remains unclear pending further screening and treatment studies; recommendations for routine anal Pap smear screening are not currently part of national guidelines. If anal cytology is performed, it is critical to refer for further evaluation of abnormal screening (e.g., high-resolution anoscopy, biopsy) and treatment.

At a minimum, consider anal cytology in women with a history of abnormal cervical cytology and/or genital warts.

The approach suggested by experts in this field is similar to recommendations for cervical Pap-smear screening: perform an anal Pap as part of the initial evaluation; if results are normal, repeat in 6 months and annually thereafter. More-frequent anal Pap smears should be considered with a previous abnormal anal Pap smear and after treatment for anal dysplasia. Anal Pap smears with ASCUS or SIL should be evaluated with high-resolution anoscopy and biopsy.

Anal Pap smears are performed by inserting a moistened Dacron swab 1–1.5 inches into the anal canal and rotating it while slowly withdrawing it over 15–20 seconds and maintaining contact with the mucosa. Both rectal columnar and anal squamous cells must be obtained to have an adequate specimen. The swab should then be vigorously shaken in liquid-based cytology media.

Management of Cervical and Other Lower-Genital-Tract Dysplasia

Management of abnormal Pap smears is outlined in Table 6-2. The purpose of colposcopy is to identify abnormal areas and their extent for targeted biopsy. The results of Pap smear plus colposcopy and/or biopsy are used to determine the need for treatment, follow-up, or further evaluation.

Treatment is recommended with documentation of a high-grade cervical lesion on biopsy; standard excisional or ablative treatment is recommended. Cryotherapy has had the highest rate of recurrence and should be avoided if other treatment methods are available. Close observation should be considered for management of CIN 1 and CIN 2 in HIV-infected adolescents. Hysterectomy should be used as treatment for high-grade cervical dysplasia

only after excluding invasive cancer with an excisional treatment and in general should not be used as a primary treatment. It is generally reserved for persistent or recurrent high-grade disease. Hysterectomy as treatment for recurrent or persistent cervical dysplasia has also been associated with significant rates of vaginal recurrence (*Am J Obstet Gynecol* 2002;186:880).

HIV infected women have an increased incidence (>50%) of recurrence of cervical lesions after treatment (*Int J STD AIDS* 2006;17(8):507), particularly with any of the following:

- Positive surgical margins with a loop electrosurgical excision procedure or cervical conization (present in >40% of HIV infected women) (*Am J Obstet Gynecol* 1999;181(6):1395; *Gynecol Oncol* 2005;96(1):112; *Int J Gynaecol Obstet* 2009;104:100)

- Glandular involvement (*Int J Gynaecol Obstet* 2009;104:100)

- Greater level of immunosuppression (*Gynecol Oncol* 1999;74:428; *J Obstet Gynaecol* 2008;28(3):327)

- Absence of suppressive ART (*Am J Obstet Gynecol* 2001;184(4):538)

Most recurrences appear to be low-grade disease, which may be associated with new HPV infections (*J Low Genit Tract Dis* 2007;11:90), but re-excision may be necessary in some cases (*Gynecol Oncol* 1999;74:428; Anticancer Res 2007;27:1795). Follow-up with cervical cytology alone or cytology and colposcopy together at 6-month intervals during the first year after treatment is recommended (*Am J Obstet Gynecol* 2007;197(4):346).

After treatment for cervical dysplasia, abstinence should be emphasized until complete healing has occurred because treatment has been shown to dramatically increase genital-tract HIV shedding, which may increase risk for sexual transmission of HIV (*Am J Obstet Gynecol* 2001;184(3):279).

Table 6-2

Recommended Management for Abnormal Pap Smear*

Pap Smear Result	Management
Unsatisfactory	• Repeat Pap smear
Partially obscuring (inflammation)	• Evaluate for infection • Consider repeat Pap smear
Epithelial Cell Abnormalities	

Atypical glandular cells	• Colposcopy, endocervical sampling
	• Endometrial sampling if aged >35 y or with abnormal bleeding
	• If AGC, favor neoplasia: cervical conization if initial evaluation is negative
	• If AGC-NOS:
	  - Consider cervical conization
	  - If observation is elected, repeat Pap smear and/or colposcopy in 6 mo
	  - If persistent reading of AGC, proceed to diagnostic excision

Table 6-2   *continued*

Recommended Management for Abnormal Pap Smear*

Pap Smear Result	Management
Atypical squamous cells (ASCUS and ASCUS-H)	• Colposcopy (repeat cytology alone in 6–12 mo can be considered for ASCUS) • Biopsy if indicated • Endocervical sampling if unsatisfactory colposcopy • Follow with Pap smear every 6 mo • Consider repeat colposcopy annually if Pap smear is unchanged • May resume annual Pap smears after two successive negative results
Low-grade squamous intraepithelial lesion (LSIL, CIN 1)	• Colposcopy • Biopsy if indicated • Endocervical sampling if unsatisfactory colposcopy • Follow with Pap smear every 6 mo • Consider annual repeat colposcopy if Pap smear is unchanged
High-grade squamous intraepithelial lesion (HSIL, CIN 2–3, carcinoma in situ)	• Colposcopy • Biopsy • Endocervical sampling • Treat with loop excision or conization • If evaluation is negative, consider diagnostic excision • If close follow-up is elected, repeat Pap smear and colposcopy in 6 mo • Proceed to excisional procedure with repeat reading of HSIL
Invasive carcinoma	• Colposcopy with biopsy or conization for diagnosis • Treat confirmed invasive disease with surgery or radiation • Referral to gynecologic oncologist

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

*Management should be based on histologic findings when biopsy is performed

Management of other lower-anogenital-tract dysplasia: Women with documented vaginal, vulvar, or anal dysplasia should be managed in consultation with a specialist. Treatment options include observation, excision, cavitational ultrasonic surgical aspiration, or laser vaporization; 5-FU has been used successfully to treat vulvar and vaginal lesions and small studies suggest a possible role for topical 1% cidofovir gel with lower-genital-tract HPV-related lesions (*J Med Virol* 2001;64:195; *Clin Infect Dis* 2001;33:597). Regardless of the type of treatment, recurrence rates are higher in HIV infected women than in uninfected women and close follow-up is needed (*Dis Colon Rectum* 2002;45:453).

Prevention of Human Papillomavirus Infection

HPV vaccine: Use of the HPV vaccine is an issue of concern in HIV infected adolescents, a significant percentage of whom were infected perinatally. Although the safety of the HPV quadrivalent vaccine has been demonstrated in HIV infected children, the efficacy of currently available HPV vaccines in HIV infected women or girls has not yet been established (*J Acquir Immune Defic Syndr* 2010;55(2):197). Given existing evidence that the vaccine is safe and immunogenic, and because of the potential benefit in preventing HPV-associated disease and cancer in HIV-infected women, either the bivalent or quadrivalent HPV vaccine is recommended for HIV-infected females aged 13 through 26 years. (MMWR *Recomm Rep* 2007;56(RR-2):1; *Obstet Gynecol* 2010;116;800; Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013)).

Condoms: Consistent and correct use of condoms has been associated with a reduced risk of acquiring genital HPV infection (including genital warts), CIN, and cervical cancer (*N Engl J Med* 2006;354:2645; *Cancer Epidemiol Biomarkers Prev* 2006;15:326; *Sex Transm Dis* 2002;29:725), although data are limited in the HIV setting.

Genital Ulcers

The presence of genital ulcers in HIV infected patients increases HIV shedding, which may increase the risk of HIV transmission to partners and also increases vulnerability to HIV acquisition (*Curr Infect Dis Rep* 2008;10:505). History, physical examination, and evaluation for patients with HIV ulcers are outlined below.

History, Physical Exam, Evaluation, and Differential Diagnosis

History

- Duration and location of lesion(s)
- Previous history of genital ulcers, syphilis, or genital herpes
- Associated symptoms, e.g., pain, pruritus, fever
- Medications and timing of ulcers relative to initiation of new medication
- Sexual history (including condom use)
- CD4+ cell count
- HIV VL

Physical Examination

- Dimensions and location of lesion(s)
- Presence of pigmentation, edema, erythema, or induration
- Presence of associated exudate or tenderness
- Presence of oral lesions
- Associated lymphadenopathy or rash

Evaluation

- Syphilis serology or darkfield examination
- Culture or PCR from lesion for herpes simplex virus (HSV); in some circumstances (e.g., genital ulcers and negative evaluation), consider type-specific HSV antibody test
- Biopsy with unclear diagnosis, lack of response to treatment: consider special stains (e.g., CMV acid-fast bacillus)
- Culture for *Haemophilus ducreyi*: not widely available commercially; diagnosis of chancroid generally made with typical clinical presentation, after excluding syphilis and HSV

Differential Diagnosis

- Infectious causes
  - HSV
  - Syphilis
  - Chancroid
  - CMV
  - Other (lymphogranuloma venereum, granuloma inguinale, TB)

- Noninfectious causes
  - Inflammatory conditions (Crohn's disease, Behçet's syndrome, hidradenitis suppurativa)
  - Neoplasia
  - Drug reaction
  - Trauma
  - Aphthous genital ulcerations

Herpes Simplex Virus

HSV is the most prevalent infectious cause of genital ulcers in the United States. Two distinct serotypes exist: HSV-1 and HSV-2; most cases of recurrent genital herpes (60%–95%) are caused by HSV-2, but HSV-1 is causing an increasing proportion of first episodes of anogenital herpes in some populations, including young women (*Sex Transm Infect* 2009;85:416). Since the late 1970s, the seroprevalence of HSV-2 infection has increased by 30%; infection is detectable in 21.9% of people aged ≥12 years nationwide (*N Engl J Med* 1997;337(16):1105). Most people with HSV-2 do not know they are infected because they have mild or unrecognized symptoms; they may, however, shed virus intermittently in the genital tract and transmit infection to their sexual partners. Age-adjusted HSV-2 prevalence is significantly higher among women than men (*J Infect Dis* 2002;185(8):1019). Viral shedding and sexual transmission can occur during asymptomatic periods.

HSV in HIV infected patients: Approximately 70% of HIV infected patients are co-infected with HSV-2 (*JAMA* 2006;296:964). More-frequent, prolonged, and/or severe episodes are common with progressive immunosuppression and lesions may be atypical in appearance or location.

HSV viral shedding, which increases with declining CD4+ cell counts (*Ann Intern Med* 1995;123:845) and higher plasma HIV VL (*Clin Infect Dis* 2003;36:207), may be more common in women who use oral contraceptives or DMPA and in women with severe vitamin A deficiency (*J Infect Dis* 2000;181:58). Most viral shedding is asymptomatic.

Although ART reduces the severity and frequency of symptomatic genital herpes, HIV infected women have comparatively more genital ulcers, and frequent subclinical shedding still occurs among women on ART (*J Infect Dis* 2004;190:693; *AIDS* 2006;20:1051). HSV is associated with increased risk for HIV transmission and/or acquisition (*Lancet* 1994;343:255) and HIV disease progression is increased by HSV-2 infection (*PLoS One* 2010;5:e9973). Higher levels of cervical HSV have been associated with increased HIV shedding in the genital tract (*AIDS* 2002;16:2425) and plasma HIV VL is increased during HSV reactivation (*J Infect Dis* 2002;186:1718)

Diagnosis: Lesions typically present as painful vesicles that ulcerate and heal without scarring. Primary infection is often associated with systemic symptoms (fever, photophobia, headache); duration of lesions and viral shedding are more prolonged with primary infection. After the primary episode, latency is established in sacral dorsal root ganglia. Recurrent episodes occur with variable frequency and are associated with more localized lesions and shorter duration than primary or nonprimary first episodes.

Nonprimary first-episode herpes, which is often milder and shorter in duration, is diagnosed with antibodies to HSV-2 or HSV-1 in patients who present with symptoms but have no previous clinical symptoms of HSV.

Treatment: Recommended HSV treatment regimens are outlined in Table 6-3. HIV infected women often need higher doses and longer courses of treatment, particularly with more advanced immunosuppression, and they may benefit from suppressive therapy. Daily suppressive therapy reduces the frequency of recurrences by ≥75% among patients who suffer from six or more HSV recurrences per year. Suppressive therapy reduces but does not eliminate viral shedding. Suppressive or episodic therapy with oral antiviral agents is effective in decreasing genital ulcers and genital HSV-2 shedding as well as genital HIV shedding and plasma HIV VL among co-infected women (*AIDS* 2009;23:461; *J Acquir Immune Defic Syndr* 2008;49:77; *N Engl J Med* 2007;356:790; *AIDS* 2006;20:2305; *Int J STD AIDS* 2002;13(1):12; *J Infect Dis* 2003;188:1009). Daily HSV suppressive therapy in HSV-2/HIV co-infected persons was not associated with reduced HIV transmission to HIV uninfected sexual partners, despite a reduction in HIV VL and occurrence of genital ulcers due to HSV-2 (*N Engl J Med* 2010;362(5):427). Clinical manifestations of genital herpes might worsen during immune reconstitution after initiation of ART.

Table 6-3	
Recommended Treatment for Herpes Simplex Virus	
Indication	**Treatment Options**
First clinical episode	• Acyclovir 400 mg po tid x 7–10 d or 200 mg po 5x/d x 7–10 d • Famciclovir 250 mg po tid x 7–10 d • Valacyclovir 1 g po bid x 7–10 d
Recurrent episodes	• Acyclovir 400 mg po tid x 5–10 d • Famciclovir 500 mg po bid x 5–10 d • Valacyclovir 1 g po bid x 5–10 d
Daily suppressive therapy	• Acyclovir 400–800 mg po bid–tid • Famciclovir 500 mg po bid • Valacyclovir 500 mg po bid
Severe disease	• Acyclovir 5–10 mg/kg body weight IV q8h x 2–7 d or until clinical improvement is observed • Follow with oral antiviral therapy to complete at least 10 d total therapy
Acyclovir-resistant HSV	• Intravenous foscarnet: 40 mg/kg IV q8h or 60 mg/kg IV q12h until clinical resolution • Intravenous cidofovir: 5 mg/kg q wk • Topical cidofovir gel 1%: apply to lesions qd x 5 consecutive days • Topical imiquimod: apply to lesions qd x 5 consecutive days

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

6

Acyclovir resistance: Suspect acyclovir resistance if lesions persist or recur in a patient on antiviral treatment; obtain a viral isolate for sensitivity testing (*Arch Intern Med* 2003;163:76). Acyclovir-resistant HSV strains are cross-resistant to valacyclovir and usually to famciclovir. The prevalence of resistant HSV in immunocompromised patients has remained stable at approximately 4%–7% (*Clin Microbiol Rev* 2003;16:114). Most of these isolates are susceptible to intravenous (IV) foscarnet or topical cidofovir. Factors associated with acyclovir resistance are low CD4+ cell counts and long-term exposure to acyclovir. Results of a study of immunocompromised but HIV uninfected patients showed that daily suppressive antiviral therapy was less likely than episodic therapy during outbreaks to be associated with the development of acyclovir-resistant HSV (*J Infect Dis* 2007;196:266).

Syphilis

Syphilis is a systemic disease caused by infection with *Treponema pallidum*.

Syphilis in HIV infected patients: HIV infected patients may have abnormal serologic test results (unusually high titers, false negatives, delayed seroreactivity). Generally, however, serologic tests can be interpreted in the usual manner. If clinical findings suggest syphilis but serology is nonreactive, then biopsy, darkfield examination, or PCR 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 disease. HIV infected patients with primary syphilis are more likely than HIV uninfected patients to have multiple ulcers and those with secondary syphilis are more likely to have concomitant genital ulcers (*Sex Transm Dis* 2001;28:158; *MMWR Recomm Rep* 2010;59(RR-12):1).

The CDC recommends annual screening for syphilis among sexually active HIV infected women, with more-frequent screening if indicated by symptoms or risk behaviors (*MMWR Recomm Rep* 2010;59(RR-12):1). Although some study results indicate no influence of HIV serostatus on rates of successful syphilis treatment (*Sex Transm Dis* 2006;33:151), others indicate significantly more treatment failures or a longer median time to successful serologic response in HIV infected patients (*Sex Transm Infect* 2007;83(2):97; *Int J STD AIDS* 2007;18:814). Close follow-up after treatment is essential.

Neurosyphilis should be considered in the differential diagnosis of neurologic signs or symptoms in HIV infected patients, who may be at increased risk for neurologic complications in early syphilis (*MMWR Morb Mortal Wkly Rep* 2007;56:625). Clinical and cerebrospinal fluid (CSF) abnormalities consistent with neurosyphilis are most likely in HIV infected patients who have been diagnosed with syphilis and have a CD4+ cell count of ≤350 cells/mm^3 and/or a rapid plasma reagin (RPR) titer of ≥1:32 (*J Infect Dis* 2004;189:369; *Sex Transm Dis* 2007;34:141; *Clin Infect Dis* 2009;49:162).

Diagnosis: Definitive methods for diagnosing early syphilis are darkfield examination and PCR (not commercially available) of lesion exudate or tissue. Presumptive diagnosis is possible using two types of serologic tests: nontreponemal (venereal disease reaction level or RPR) and a confirmatory treponemal test (fluorescent treponemal antibody absorption test, microhemagglutination-*T. pallidum*, various enzyme immunoassays [EIAs], and chemiluminescence immunoassays). Nontreponemal antibody titers usually correlate with disease activity and are used to assess treatment response. Serial assessment during follow-up after treatment should use the same type of nontreponemal test.

Treatment: Recommended management strategies are outlined in Table 6-4. ART may improve clinical outcomes in patients co-infected with HIV and syphilis (*Clin Infect Dis* 2008;47:893; *AIDS* 2008;22:1145; *Clin Infect Dis* 2008;47:258).

Table 6-4

Recommended Treatment of Syphilis

Syphilis Stage	Treatment
Primary, secondary, and early latent	• Benzathine penicillin G, 2.4 million units IM (single dose) • CSF examination indicated with neurologic signs/symptoms • Routine CSF exam not associated with improved clinical outcomes • If penicillin-allergic: consider skin testing and PCN desensitization if positive
Late latent, unknown duration, and tertiary	• Benzathine penicillin G, 7.2 million units IM; administer as 2.4 million units q wk x 3 wk • CSF examination indicated with neurologic signs/symptoms • Routine CSF exam not associated with improved clinical outcomes
Neurosyphilis	• Aqueous crystalline penicillin G, 18–24 million units qd; administer as 3–4 million units IV q4h or by continuous infusion x 10–14 d • Some recommend benzathine penicillin 2.4 million units IM q wk x 1–3 wk after completion of IV regimen

Recommended Follow-up for Management of Syphilis

Syphilis Stage	Treatment
Primary, secondary	• HIV infected patients: clinical and serologic evaluation for treatment failure at 3, 6, 9, 12, and 24 mo after treatment • Treatment failure (with signs or symptoms that persist or recur or sustained fourfold increase in nontreponemal test titer): CSF examination; if CSF exam is negative, retreat with benzathine penicillin G, 2.4 million units IM q wk x 3 wk; consider same for patients whose titers do not decrease fourfold within 6–12 mo
Latent	• HIV infected patients: clinical and serologic evaluation at 6, 12, 18, and 24 mo after treatment • With development of clinical symptoms, fourfold rise in titers, or titers that do not decrease fourfold between 12 and 24 mo after evaluation, perform CSF examination and follow with appropriate treatment
Neurosyphilis	• Repeat CSF examination q 6 mo until cell count is normal • Consider retreatment if cell count has not decreased after 6 mo or if CSF is not entirely normal after 2 y • Limited data suggest that changes in CSF parameters might occur more slowly in HIV infected patients, especially those with more advanced immunosuppression (AIDS 2008;22:1145)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

6

Chancroid

Chancroid is caused by infection with *Haemophilus ducreyi*, which is endemic in some areas of the United States and also occurs in discrete outbreaks. Ten percent of patients with chancroid are co-infected with *T. pallidum* or HSV.

Chancroid in HIV infected patients: Response to treatment may be diminished in HIV infected patients, who may require longer or repeated courses of therapy and may be at increased risk for treatment failure.

Diagnosis: The initial presentation typically consists of a tender papule that becomes pustular and then ulcerative; the ulcer is usually well demarcated, with ragged, undermined edges. Definitive diagnosis requires the identification of *H. ducreyi* on special culture media (not widely available; sensitivity <80%). No U.S. Food and Drug Administration (FDA)-cleared PCR test for *H. ducreyi* is available in the United States. A probable diagnosis can be made if the patient has one or more painful ulcers, no evidence of *T. pallidum* or HSV infection is apparent, and the clinical presentation (appearance of ulcers and regional lymphadenopathy) is typical for chancroid.

Treatment: In HIV infected patients, single-dose therapies should be used only if follow-up can be ensured. Recommended regimens include the following (*MMWR Recomm Rep* 2010;59(RR-12):1):

- Azithromycin 1 g po (single dose), *or*
- Ceftriaxone 250 mg intramuscularly (IM) (single dose), *or*
- Ciprofloxacin 500 mg po bid x 3 days, *or*
- Erythromycin base 500 mg po 4x/day x 7 days

Cytomegalovirus

CMV should be suspected with genital ulcers in severely immunocompromised patients. Cervical shedding of CMV is associated with low CD4+ cell counts (*J Acquir Immune Defic Syndr Hum Retrovirol* 1997;15:341).

Diagnosis: Biopsy of lesion with immunohistochemical stains is required.

Treatment: Ganciclovir 5 mg/kg IV bid x 3–4 weeks or foscarnet 60 mg/kg IV q8h or 90 mg/kg q12h for 3–4 weeks.

Other Infectious Causes of Genital Ulcers

Lymphogranuloma venereum: Infection is rare in the United States and is associated with tender, usually unilateral inguinal or femoral lymphadenopathy, proctocolitis, or rectal fistulas/strictures. Diagnosis is made with serology and exclusion of other causes. Treatment is a 3-week course of doxycycline or erythromycin. HIV infected patients may require more-prolonged treatment and resolution of symptoms may be delayed.

Granuloma inguinale (donovanosis): Infection is rare in the United States. It is associated with painless, progressive ulcers that bleed easily on contact, without regional lymphadenopathy. Diagnosis is made with biopsy or tissue-crush preparation. Treatment options are doxycycline, azithromycin,

ciprofloxacin, erythromycin, or trimethoprim-sulfamethoxazole, taken for 3 weeks or until all lesions are healed. The CDC recommends considering the addition of aminoglycoside to the treatment regimen in HIV infected patients.

Tuberculosis: Genital TB is generally a secondary manifestation of primary disease, usually pulmonary. In the United States, the incidence of genital disease is <1%. Diagnosis is made with biopsy. Genital TB should be treated in the same manner as extrapulmonary disease; expert consultation is necessary (*Eur J Obstet Gynecol* Reprod Biol 1998;80(2):227).

Noninfectious Causes of Genital Ulcers

Crohn's disease: This disease is easy to misdiagnose because its principal clinical features (fever, abdominal pain, diarrhea, fatigability, weight loss) are often found in patients with HIV infection. Crohn's disease may also present with genital ulcers, rectal fissures, perirectal abscesses, or intestinal fistulas. Sigmoidoscopy or barium enema is essential in making this diagnosis. Manage with expert consultation.

Behçet's syndrome: This is a multisystem disorder that presents with recurrent oral and genital ulcerations as well as uveitis, arthritis, and vasculitis. Vaginal ulcers are usually painless, whereas lesions on the external genitalia are generally painful. Ulcers range between 2 mm and 10 mm in diameter and can be shallow or deep, with a central yellowish necrotic base. A single lesion or crops of lesions may be evident. Diagnosis is established on the basis of the clinical presentation and biopsy. Treatment consists of topical or systemic corticosteroids.

Hidradenitis suppurativa: This is a chronic, refractory condition involving the skin, subcutaneous tissues, and apocrine glands. Lesions are painful and are associated with a foul-smelling discharge. Eventually a deep-seated chronic infection of the apocrine glands develops, with multiple draining abscesses and sinuses. A biopsy is necessary to establish the diagnosis. In the early stages of disease, treatment options include antibiotics, anti-androgens, and retinoids. Treatment of advanced disease requires surgical intervention (*Dermatol Clin* 2010;28:779).

Neoplasia: Any nonhealing genital ulcer must be biopsied to rule out a neoplastic process, including squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, melanoma, lymphoma, and Kaposi's sarcoma. Refer to an oncologist for management.

Drug reaction: Genital ulcers have been described as a rare side effect of treatment with zalcitabine and foscarnet.

Trauma: Consider with a history of traumatic injury and the possibility of sexual violence.

Aphthous genital ulcerations: Aphthous genital ulcers have no identifiable specific etiology (typical or opportunistic organism) and are similar to aphthous ulcers seen in the gastrointestinal tract (*J Acquir Immune Defic Syndr Hum Retrovirol* 1996;13(4):343). Most patients with these types of ulcers

6

are significantly immunosuppressed (median CD4+ cell count 50 cells/mm^3). Oro-esophageal ulcers coexist in about one-third of cases, and one-fifth are associated with genital fistula formation.

The lesions can be painful, multiple, deep, and extensive (1–6 cm). Associated morbidity includes immobility, bleeding, and superinfection. Most have been reported to be chronic and/or recurrent or relapsing.

Treatment: After standard evaluation for other causes, consider empiric therapy for HSV. If empiric therapy fails, systemic steroids (prednisone 40–60 mg/day for 1–2 weeks, then taper) have been moderately successful. There has been one report of successful treatment of oral aphthous ulcers with ART (*Int J Infect Dis* 2007;11(3):278).

Thalidomide: Thalidomide 200 mg qd x 2–4 weeks has been used to treat similar ulcers in the oropharynx or esophagus, with complete healing in 55%–73% of cases (*N Engl J Med* 1997;336:1487; *J Infect Dis* 1999;180:61). There are anecdotal reports of similar success in treating genital aphthous ulcers. **WARNING:** Thalidomide is a powerful teratogen and should be used by women of reproductive age only after appropriate counseling and pregnancy testing and in the setting of reliable contraception or abstinence.

Vaginal Discharge

Abnormal vaginal discharge is a common gynecologic complaint among women, including HIV infected women.

History, Physical Exam, Evaluation, and Differential Diagnosis

History

- Duration and characteristics of discharge
- Associated symptoms (e.g., pruritus, malodor, burning, pelvic pain)
- Associations with menstrual cycle
- Sexual history, including condom and other contraceptive use
- History of sexually transmitted diseases
- History of douching
- Recent antibiotic use
- CD4+ cell count
- HIV VL
- Medications

Physical Exam

- Complete genital inspection and bimanual pelvic examination
- Document characteristics and amount of discharge as well as presence of erythema, edema, and tenderness

Evaluation

- Saline wet mount
- 10% potassium hydroxide (KOH) preparation
- Vaginal pH determination
- Test for gonorrhea and chlamydia
- Perform fungal culture if indicated (signs/symptoms of yeast infection with negative findings on microscopy; chronic/recurrent yeast infections)

Differential Diagnosis

- Bacterial vaginosis (BV)
- Vulvovaginal candidiasis
- Trichomoniasis
- Gonorrhea
- Chlamydia
- Other causes of abnormal vaginal discharge

6

Bacterial Vaginosis

BV is the most prevalent cause of vaginal discharge or malodor. It results from the replacement of normal *Lactobacillus*-dominant vaginal flora with mixed flora, including anaerobic bacteria, *Gardnerella vaginalis*, and *Mycoplasma hominis*. It is associated with increased rates of several obstetric and gynecologic complications, including pelvic inflammatory disease (PID), postabortion and posthysterectomy infections, and preterm labor. BV increases the risk of HIV-1 acquisition in women (*AIDS* 2008;22(12):1493; *J Infect Dis* 2005;192(8):1372) and increases HIV-1 shedding in the genital tract (*J Infect Dis* 2005;191(1):25).

Bacterial vaginosis in HIV infected patients: Data conflict on whether HIV infection is associated with increased BV prevalence compared with high-risk uninfected women (*Obstet Gynecol* 2001;98(4):656; *J Acquir Immune Defic Syndr* 2006;43:161). One study found both increased prevalence of BV and increased bacterial persistence in HIV infected women; increased persistence could result in higher prevalence, but not necessarily more frequent infections (*Obstet Gynecol* 2001;98(4):656). Prevalence, persistence, and severity all increase as CD4+ cell counts decrease (*Obstet Gynecol* 2001;98(4):656; *Clin Infect Dis* 1999;29:1145; *Sex Transm Dis* 1999;26:143). Use of ARVs has been associated with lower BV prevalence (*Infect Dis Obstet Gynecol* 2001;9:133).

Diagnosis: Standard diagnosis is made by clinical criteria and requires the presence of three of the following: 1) homogeneous grayish or yellowish discharge that may coat vaginal walls; 2) clue cells on microscopic examination; 3) vaginal pH >4.5; and/or 4) a positive whiff test (i.e., fishy odor of discharge before or after addition of 10% KOH).

Treatment: Treatment is indicated for women who have symptoms of BV. No current data suggest that screening and treatment of asymptomatic women reduces obstetric or gynecologic complications. A Pap smear report of "bacterial flora shift suggestive of BV" does not indicate treatment, but does indicate the need to question the patient about signs or symptoms.

Recommended regimens include the following (*MMWR Recomm Rep* 2010;59(RR-12):1):

- Metronidazole 500 mg po bid x 7 days (avoid alcohol during treatment and for 24 hours after completion), *or*
- Clindamycin cream 2%, 5 g intravaginally qhs x 7 days (oil based and may weaken latex condoms and diaphragms), *or*
- Metronidazole gel 0.75%, 5 g intravaginally qd x 5 days

Alternative regimens include the following (*MMWR Recomm Rep* 2010;59(RR-12):1):

- Tinidazole 2 g qd x 2 days, *or*
- Tinidazole 1 g qd x 5 days, *or*
- Clindamycin 300 mg po bid x 7 days, *or*
- Clindamycin ovules 100 g intravaginally qhs x 3 days

Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is most commonly caused by infection with *Candida albicans*; however, the prevalence of infections due to non-*albicans* species is increasing. Up to 75% of all women will have at least one episode of candidiasis and 40%–45% will have two or more episodes; fewer than 5% of women experience recurrent episodes of candidiasis.

Typical symptoms are a thick, white discharge and pruritus; other symptoms include vulvar burning, vaginal soreness, dyspareunia, and external dysuria.

Vulvovaginal candidiasis in HIV infected patients: VVC is associated with increased HIV seroconversion in women who are not HIV infected and with increased genital tract HIV in HIV infected women (*Sex Transm Dis* 2008;35(11):946; *J Acquir Immune Defic Syndr* 2008;48(2):203).

Prevalence among HIV-infected women is 3%–15%; most studies suggest no significant difference in the prevalence of infection between relatively immunocompetent HIV infected women and uninfected controls. Analysis of longitudinal data from HERS indicated that VVC occurred with higher incidence and greater persistence, but not greater severity, among HIV infected women compared with uninfected women. A lower CD4+ cell count and higher VL were associated with VVC (*Clin Infect Dis* 1999;29:1145; *Obstet Gynecol* 2003;101:548). More-frequent use of antibiotics is a possible confounding factor for HIV infected women and pregnancy is a predisposing factor for candidiasis irrespective of HIV status.

Most studies show increased rates of vaginal, rectal, and oral colonization in HIV infected women, particularly with declining immune function (*J Acquir Immune Defic Syndr* 2006;43:161; *J Infect Dis* 2003;188:118; *Obstet Gynecol* 1997;90(2):252; *Obstet Gynecol* 2003;101:548). In HIV infected women, 26%–27% of vaginal isolates are non-*albicans* strains (*Clin Infect Dis* 1998;27:1161); although the most common strain is C. *glabrata*, data conflict on the proportion of non-*albicans* strains in HIV infected women compared with uninfected women. No association has been found between strain diversity and HIV progression.

Diagnosis: Diagnosis is made by identifying budding yeast or pseudohyphae on a wet mount, KOH preparation, or Gram stain of vaginal discharge. Positive identification can also be accomplished with culture. In general, wet mount and KOH are used as point-of-care tests if microscopy is available. Culture is usually reserved for cases of unclear diagnosis or for species identification in recurrent and/or persistent cases.

Treatment: Table 6-5 details recommended treatment regimens. In general, conventional antifungal therapies are less effective with non-*albicans* species; 10–14 days of therapy with a non-fluconazole azole drug is recommended as first-line therapy.

6

Table 6-5

Management of Vulvovaginal Candidiasis

Agent	Dosing and Notes
Topical Azoles	
Butoconazole	• 2% cream* 5 g vaginally x 3 d • 2% single-dose bioadhesive 5 g: one vaginal application
Clotrimazole	• 1% cream* 5 g vaginally x 7–14 d • 2% cream* 5 g vaginally x 3 d
Miconazole	• 2% cream* 5 g vaginally x 7 d • 4% cream* 5 g vaginally x 3 d • 200 mg vaginal suppository* qd x 3 d • 100 mg vaginal suppository* qd x 7 d • 1200 mg vaginal suppository* (one application)
Tioconazole	• 6.5% ointment* 5 g vaginally (one application)
Terconazole	• 0.4% cream* 5 g vaginally x 7 d • 0.8% cream* 5 g vaginally x 3 d • 80 mg vaginal suppository qd x 3 d
Oral Agent	
Fluconazole	• 150 mg single dose po; avoid concomitant use with terfenadine, astemizole, and cisapride secondary to cardiotoxicity

Table 6-5	*continued*

Management of Vulvovaginal Candidiasis

Agent	Dosing and Notes
Other Agents	
Nystatin	• 100,000-unit vaginal tablet qd x 14 d; less effective than other treatments
Gentian violet	• 1% for vaginal application q7d x 4; messy; may be useful in chronic or recurrent cases; causes mucosal exfoliation; encourage abstinence during treatment; reinforce condom use
Boric acid	• 600 mg intravaginal capsules qd x 14 d; may be useful in chronic or recurrent cases; encourage abstinence during treatment; reinforce condom use

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

*Available over the counter

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

Special treatment considerations for HIV infected women

- Topical therapies may be more effective when given for at least 7 days; fluconazole may be more effective when given in two sequential 150-mg doses 3 days apart (*Adv Stud Med* 2005;5:403)

- Consider prophylactic use of topical antifungals when antibiotics are given

- Long-term prophylactic therapy with fluconazole at a dose of 200 mg weekly has been found effective in reducing colonization with *C. albicans* and symptomatic vulvovaginal candidiasis in HIV infected women, but this regimen is not recommended for routine primary prophylaxis in HIV infected women (*Clin Infect Dis* 2001;33:1069; *MMWR Recomm Rep* 2010;59(RR-12):1). Consider in selected cases with recurrent vaginal candidiasis.

Azole resistance: There is some concern that extensive use of oral azoles may promote azole resistance and possibly limit the use of these agents for other HIV-related indications. Information about reduced azole susceptibility is limited but suggests that it is relatively uncommon with *C. albicans* isolates, with no evidence of a progressive reduction in susceptibility over time. Among non-*albicans* isolates, reduced susceptibility occurs frequently and is more common among HIV-seropositive women (*J Infect Dis* 2001;183(2):286; *Rev Iberoam Micol* 2004;21(4):177; *Ann Intern Med* 1997;126:689). No current data suggest that intermittent therapy with a single dose of fluconazole increases the development of azole resistance. Weekly prophylaxis with fluconazole has been associated with the infrequent development of resistance (*Ann Intern Med* 1997;126:689). Nevertheless, long-term treatment with fluconazole may select for more resistant and difficult-to-treat non-*albicans* species and should be used with caution.

Recurrent Candidiasis

Four or more symptomatic episodes of candidiasis per year are considered recurrent candidiasis. Evaluation includes identification and/or elimination (if possible) of predisposing factors that may include uncontrolled diabetes, corticosteroid use, topical or systemic antibiotics, spermicides (conflicting data), tight-fitting synthetic underwear, douching, pregnancy, and immunosuppression.

Diagnosis: Fungal culture may be needed if the diagnosis is unclear, symptoms are recurrent or persistent, and wet mount and/or KOH or Gram stain are negative. Speciation and/or susceptibility testing may be required.

Treatment: Management options include the following:

- Longer duration of standard treatment regimen (e.g., 7–14 days of topical therapy; fluconazole 100 mg, 150 mg, or 200 mg every third day for total of three doses)

- Chronic intermittent therapy (e.g., with perimenstrual episodes)

- Restriction of orogenital and/or anogenital sexual contact (anecdotal evidence only; double-blind, placebo-controlled trials of topical therapy for male sexual partners showed no benefit [*Sexually Transmitted Diseases*. 4th ed. New York: McGraw Hill; 2008])

- Possible role for boric acid vaginal capsules and gentian violet (*Gynecol Obstet Invest* 2010;70:306)

- Maintenance therapy, comprising an initial intensive regimen followed by one of the following maintenance regimens for at least 6 months: fluconazole 100, 150, or 200 mg po weekly (avoid concomitant use with terfenadine, astemizole, cisapride secondary to cardiotoxicity) *or* clotrimazole 500 mg vaginal suppository weekly

- Immune reconstitution: ART initiation has potential benefit if indicated (*J Infect Dis* 1999;180:448)

Trichomoniasis

Trichomoniasis is caused by infection with *Trichomonas vaginalis*. Clinical features include profuse, malodorous, often frothy, yellow-green discharge and vulvar irritation, which may be accompanied by urinary symptoms or dyspareunia and signs of inflammation (i.e., vaginal erythema, "strawberry" vagina, cervix with punctate hemorrhages). In chronic cases, infection may be asymptomatic.

Trichomoniasis in HIV infected patients: In HIV infected women *T. vaginalis* infection increases genital HIV shedding and possibly sexual and perinatal transmission. Treatment of *T. vaginalis* has been shown to reduce HIV shedding (*J Infect Dis* 2003;187:375; *J Infect Dis* 2001;183:1017; *Sex Transm Dis* 2009;36:11; *J Perinatol* 2010;30(11):717). Trichomoniasis has also been associated with an increased risk of HIV acquisition (*J Infect Dis* 2008;197:548; *J Infect Dis* 2007;195:698).

In HIV infected women, trichomoniasis prevalence is 5%–23% and incidence is 10%–17% (*Am J Obstet Gynecol* 1999;180:824; *Am J Trop Med Hyg* 1998;58:495); however, studies have not shown increased prevalence, incidence, persistence, or recurrence in HIV infected women compared with either uninfected women or HIV infected women with lower CD4+ cell counts (*Clin Infect Dis* 2002;34:1406; *J Acquir Immune Defic Syndr* 2006;43(2):161).

Results of a study from South Africa indicated that trichomoniasis was associated with a significantly higher risk of PID, specifically in women with HIV (*Clin Infect Dis* 2002;34(4):519).

Diagnosis: Diagnosis is made with a variety of methods: saline wet mount (motile trichomonads seen in 50%–70% of culture-positive cases), Pap smear (60%–70% sensitivity; false positives not uncommon), culture (95% sensitivity), PCR, DNA probes, and monoclonal antibodies. Point-of-care testing with wet mount is the preferred method if microscopy is available. Other methods are useful in the absence of microscopy or with consistent symptoms and a negative wet mount result.

Treatment: Recommended regimens are outlined in Table 6-6. If sex partners are treated simultaneously, cure rates of >90% can be expected. Topical metronidazole has been found to be less effective than the oral preparation (*MMWR Recomm Rep* 2010;59(RR-12):1).

Table 6-6

Treatment of Trichomoniasis

Drug	Dosage	Comments
Metronidazole	500 mg po bid x 7 d	• More effective than single-dose metronidazole regimen in setting of HIV (*J Acquir Immune Defic Syndr* 2010;55:565) • Avoid alcohol during treatment and for 24 h after completion of therapy • Treat sex partners with same regimen; avoid intercourse until therapy is complete and patient and partner are asymptomatic
Metronidazole	2 g po (single dose)	• Avoid alcohol during treatment and for 24 h after completion of therapy • Treat sex partners with same regimen; avoid intercourse until therapy is complete and patient and partner are asymptomatic
Tinidazole	2 g po (single dose)	• No studies have evaluated tinidazole treatment in women co-infected with HIV and *T. vaginalis* • Avoid alcohol during treatment and for 72 h after completion of therapy • Treat sex partners with same regimen; avoid intercourse until therapy is complete and patient and partner are asymptomatic

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

Three months after completion of treatment, consider rescreening HIV infected women, regardless of symptoms, given the high proportion of recurrent or persistent infection and the association between HIV and *T. vaginalis* infection (*Sex Transm Dis* 2000;27:284; *Clin Infect Dis* 2008;46:994; *Ann Intern Med* 2006;145:564).

Resistance: Low-level metronidazole resistance has been identified in 2%–5% of cases of vaginal trichomoniasis (*Antimicrob Agents Chemother* 2006;50:4209), but high-level resistance occurs only rarely. Organisms with decreased susceptibility usually respond to tinidazole or to higher doses of metronidazole. If treatment failure occurs with either regimen, re-treat with metronidazole 500 mg po twice a day for 7 days. If treatment failure occurs repeatedly, treat with metronidazole or tinidazole 2 g po once a day for 5 days. Patients with documented infection (with re-infection excluded) who have not responded to these measures should be managed in consultation with an expert.

6

Gonorrhea

Gonorrhea is caused by infection with *Neisseria gonorrhoeae*. Infection is commonly asymptomatic but vaginal discharge may be present. If untreated, 10%–20% of infected women develop PID. The urethra is the primary site of colonization after hysterectomy. Gonorrhea may also cause rectal infection, pharyngitis, and (rarely) disseminated infection.

Gonorrhea in HIV infected patients: There are no differences in prevalence, clinical presentation, diagnosis, or treatment between HIV infected and uninfected patients.

Diagnosis: Diagnosis is made by nucleic acid amplification tests (NAATs) of endocervical, vaginal, or urine specimens; by nucleic acid hybridization tests of endocervical or urethral (after hysterectomy) specimens; or through culture of the endocervix or urethra (after hysterectomy). The sensitivity of NAATs for the detection of *N. gonorrhoeae* in genital and nongenital anatomic sites is superior to culture but varies by NAAT type. The NAAT may detect gonorrhea and chlamydia simultaneously. Because nonculture tests cannot provide antimicrobial susceptibility results, in cases of suspected or documented treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing (*MMWR Recomm Rep* 2010;59(RR-12):1).

Treatment: *N. gonorrhoeae* has the ability to develop antibiotic resistance, which makes it a moving target for treatment. In the United States, as of April 2007, quinolones are no longer recommended for the treatment of gonorrhea and associated conditions; cephalosporins are the only antimicrobial class currently recommended and available (*MMWR Recomm Rep* 2010;59(RR-12):1). In the United States, minimum inhibitory concentrations of *N. gonorrhoeae* to cephalosporins have been increasing—particularly for cefixime—though no resistant cases have been seen yet. The CDC is now recommending treatment of gonorrhea with single-dose ceftriaxone 250 mg IM and the ***preferential*** co-treatment of chlamydia with single-dose azithromycin 1 g po, instead of 1 week of doxycycline, because azithromycin

offers coverage of both gonorrhea and chlamydia (*MMWR Morb Mortal Wkly Rep* 2011;60(26):873). The CDC's website (http://www.cdc.gov/std/gisp) and state health departments can provide the most current information on gonorrhea treatment.

For uncomplicated gonococcal infections of the cervix, urethra, and rectum, the following regimens are recommended (*MMWR Recomm Rep* 2010;59(RR-12):1), with rescreening 3 months after treatment:

- Single-dose ceftriaxone 250 mg IM; *or*, if not an option,
- Single-dose cefixime 400 mg po (less effective for pharyngeal infection); *or*
- Single-dose injectable cephalosporin regimen *plus*, for presumptive chlamydia treatment, single-dose azithromycin 1 g po (preferred) *or*, if azithromycin is not an option, doxycycline 100 mg po bid for 7 days; *or*
- Alternative single-dose injectable cephalosporin regimens: ceftizoxime 500 mg IM, cefoxitin 2 g IM with probenecid 1 g po, and cefotaxime 500 mg IM (efficacy for pharyngeal infection is less certain)

It is recommended that women be treated for chlamydia presumptively, particularly in areas with high rates of co-infection, or where there is no chlamydia testing, and/or when a patient may not return for test results. Avoid the use of doxycycline or quinolones in pregnancy.

Treatment of sex partners: Sex partners should be treated for both gonorrhea and chlamydia if their last sexual contact with the patient was within 60 days before the diagnosis or onset of symptoms. If a patient's most recent sexual contact occurred more than 60 days before the onset of symptoms, her most recent partner should be treated. Intercourse should be avoided until treatment is completed and symptoms have resolved.

Culture and susceptibility testing are recommended after apparent treatment failure with the standard regimen; persistent positive test results with or without persistent symptoms indicate treatment failure.

Chlamydia

Chlamydia is caused by infection with *Chlamydia trachomatis*. Asymptomatic infection is common, but clinical presentation may include abnormal discharge and/or symptoms of urethritis. If untreated, 10%–40% of infected women develop PID.

Chlamydia in HIV infected patients: There are no differences in prevalence, clinical presentation, diagnosis, or treatment between HIV infected and uninfected women.

Diagnosis: NAATs, cell culture, direct immunofluorescence, EIA, and nucleic acid hybridization tests are available for the detection of C. *trachomatis* on endocervical specimens. NAATs have the highest sensitivity and can also be used with urine. Some NAATs are cleared for use with vaginal swab specimens, which can be collected by the provider or self-collected by the patient. Self-collected vaginal swab specimens perform well compared with

other approved specimens using NAATs (*Sex Transm Dis* 2005;32:725; *Int J STD AIDS* 2008;19:507) and are well accepted by women. NAATs may also be used to detect C. *trachomatis* at rectal and oropharyngeal sites and have demonstrated improved sensitivity and specificity compared with culture at these sites (*Sex Transm Dis* 2008;35:637; *J Clin Microbiol* 2010;48:1827; *J Clin Microbiol* 2009;47:902).

Treatment: Recommended regimens include the following (*MMWR Recomm Rep* 2010;59(RR-12):1), with rescreening 3 months after completion of treatment:
- Single-dose azithromycin 1 g po, *or*
- Doxycycline 100 mg po bid x 7 days (avoid in pregnancy)

Alternative regimens include the following:
- Erythromycin base 500 mg po 4x/day x 7 days, *or*
- Erythromycin ethylsuccinate 800 mg po 4x/day x 7 days, *or*
- Ofloxacin 300 mg po bid x 7 days (avoid in pregnancy), *or*
- Levofloxacin 500 mg po x 7 days (avoid in pregnancy)

Recommendations for the management of chlamydia in sex partners are the same as for gonorrhea (see above).

Other Causes of Abnormal Vaginal Discharge

Abnormal vaginal discharge may have several other potential causes.

Atrophic vaginitis: This condition, which is related to estrogen deficiency, is characterized by irritative symptoms, vaginal dryness, and dyspareunia. The vaginal epithelium appears thin and a watery discharge may be present. Treat with either topical or oral estrogen.

Foreign body: If suspected, a careful speculum exam should be performed to identify retained tampons, toilet paper, etc.

Local irritants: Remove possible offending agents, including spermicides, vaginal medications, toilet-paper dye, hygiene sprays, soap, detergent, douches, etc.

Pelvic and/or Lower Abdominal Pain

Abdominopelvic pain can be classified as acute, chronic, or cyclic. Acute pain is typically sudden in onset and short in duration, whereas chronic pain is of at least 6 months' duration. Cyclic pain is associated with the menstrual cycle.

History, Physical Exam, Evaluation, and Differential Diagnosis

History

- Characteristics of pain:
  - onset rapid or gradual
  - character crampy, colicky, sharp, or dull
  - location generalized or localized
  - duration
  - severity
  - radiation of pain
  - constant or intermittent

- Associated symptoms:
  - abnormal vaginal bleeding or discharge
  - gastrointestinal symptoms (e.g., nausea/vomiting, anorexia, constipation, diarrhea)
  - urinary symptoms (e.g., dysuria, frequency, urgency, hematuria)
  - fever or chills

- History of other medical conditions
- Surgical history
- Gynecologic history:
  - date of last menstrual period
  - use of contraception and condoms
  - history of sexually transmitted infections (STIs)

- Medications
- CD4+ cell counts
- HIV VL

Physical Exam

- Obtain complete set of vital signs
- Focus on abdominal and pelvic findings
- Abdominal exam should evaluate
  - presence and character of bowel sounds
  - presence of distention
  - suprapubic or costovertebral angle tenderness
  - other abdominal tenderness, including location, presence of rebound, and guarding
  - presence of mass or organomegaly
- Pelvic exam should determine
  - presence of abnormal bleeding or discharge
  - reproducibility and location of tenderness (e.g., uterine, adnexal, or cervical motion tenderness)
- Presence of a palpable abdominal or pelvic mass

Evaluation

- Pregnancy test
- Laboratory tests
  - CBC with differential
  - sedimentation rate or C-reactive protein
  - chemistry panel
  - others as indicated

• Wet mount and/or STI testing
• Urinalysis and urine culture
• Stool studies (cultures, evaluation for ova and parasites, *Clostridium difficile* toxin assay), if indicated by gastrointestinal (GI) symptomatology
• Pelvic ultrasound, computed tomography (CT) scans, if indicated
• Blood cultures for bacteria and/or *Mycobacterium avium*, if indicated

Differential Diagnosis

Differential diagnosis includes but is not limited to
• Pregnancy
• PID
• Ruptured/hemorrhagic ovarian cyst
• Ovarian torsion
• Uterine leiomyomas (fibroids)
• Endometriosis
• Dysmenorrhea
• Mittelschmerz
• Gastrointestinal pathology
• Urinary tract pathology
• Medication-related pathology

Pregnancy (see Chapter 8)

Refer as indicated. With pain and a positive pregnancy test with or without bleeding, suspect ectopic pregnancy; urgent evaluation is indicated.

Pelvic Inflammatory Disease

PID is an upper-genital-tract infection, usually polymicrobial in nature. Sexually transmitted organisms, including *N. gonorrhea* and *C. trachomatis*, are implicated in most cases of PID; BV-associated organisms are also commonly present. CMV, *M. hominis*, *Ureaplasma urealyticum*, and *M. genitalium* may be associated with some cases of PID (*Sex Transm Infect* 2005;81:463; *Sex Transm Infect* 2007;83:319; *Clin Infect Dis* 2009;48:417). Symptoms may be virtually absent or mild and nonspecific (e.g., abnormal bleeding, dyspareunia, vaginal discharge; less commonly, right-upper-quadrant pleuritic pain secondary to perihepatitis).

PID in HIV infected patients: Several studies have found an increased seroprevalence of HIV in patients hospitalized with PID (*Am J Obstet Gynecol* 1990;163:1135; *J Reprod Med* 1991;36:122). An analysis of hysterectomy specimens from HIV infected and uninfected women, matched for surgical indication, found chronic endometritis twice as commonly in the specimens from HIV infected women as in those from uninfected women; some degree of abnormal uterine bleeding had occurred in all cases (*Infect Dis Obstet Gynecol* 1998;6:186). The clinical presentation of PID in HIV infected women may be more severe or otherwise altered (e.g., lower white blood cell counts) (*Obstet Gynecol* 1997;89:65; *J Infect Dis* 1998;178:1352; *Am J Obstet Gynecol* 1995;172:919; *Obstet Gynecol* 2000;95:525). In studies from Africa, more-

severe illness, including tubo-ovarian abscess, and longer hospital stays were found in women with significant immunosuppression (*Am J Obstet Gynecol* 1995;172:919; *J Infect Dis* 1998;178:1352).

HIV infected and uninfected women respond equally well to standard parenteral and oral antibiotic regimens (*Obstet Gynecol* 2006;107:807; *Am J Obstet Gynecol* 1999;181:1374). The microbiology of infection and the response to standard antibiotic regimens are similar in HIV infected and uninfected women, although one study found that mycoplasmas and streptococci were more likely to be isolated from HIV infected women (*Obstet Gynecol* 2000;95:525). Some studies have reported a greater need for surgical intervention in HIV infected women (*Obstet Gynecol* 1993;82:765).

CMV, cryptococcosis, and tuberculosis may cause upper-genital-tract infection in rare cases and should be considered in appropriate clinical situations (*Infect Dis Obstet Gynecol* 2009;2009:745060; *Int J Gynecol Pathol* 2008;27(1):37).

Diagnosis: The current minimum CDC-recommended criteria for diagnosis of PID are cervical motion tenderness **or** uterine tenderness **or** adnexal tenderness (*MMWR Recomm Rep* 2010;59(RR-12):1). Because PID is difficult to diagnose and has the potential to cause long-term complications, empiric therapy should be initiated if these criteria are present and no other cause for symptoms is identified.

Criteria that enhance diagnostic specificity include
- oral temperature >101°F (>38.3°C),
- abnormal mucopurulent cervical or vaginal discharge,
- elevated erythrocyte sedimentation rate,
- elevated C-reactive protein,
- documented cervical gonorrhea or chlamydia infection, and
- elevated white blood cells on saline wet mount of vaginal secretions.

In patients who are severely ill and/or when diagnosis is uncertain, the most specific criteria for diagnosis of PID are
- endometritis on endometrial biopsy;
- tubo-ovarian complex, **or** thickened, fluid-filled tubes on transvaginal ultrasound or magnetic resonance imaging (MRI), **or** Doppler studies suggesting pelvic infection (e.g., tubal hyperemia); and
- laparoscopic abnormalities consistent with PID.

Treatment: The decision to treat with oral vs. parenteral antibiotics (Table 6-7) should be individualized, as should the decision to hospitalize an HIV infected patient with PID for treatment. Indications for hospitalization include
- inadequate response to outpatient therapy;
- uncertain diagnosis (surgical emergency cannot be excluded);
- pregnancy;
- inability to tolerate or follow outpatient regimen;

- tubo-ovarian abscess or other evidence of severe illness, nausea and vomiting, or high fever; and

- consider with immunosuppression or other significant comorbidity: low CD4+ cell count, clinical AIDS, on immunosuppressive drugs.

Table 6-7		
Parenteral Regimens for Treatment of Pelvic Inflammatory Disease		
Regimen A	Cefotetan 2 g IV q 12 h + doxycycline 100 mg po or IV q 12 h **or** Cefoxitin 2 g IV q 6 h + doxycycline 100 mg po or IV q 12 h	• Parenteral therapy may be discontinued 24 h after evidence of clinical improvement • Oral therapy with doxycycline 100 mg bid should continue through completion of 14 days of therapy • When tubo-ovarian abscess is present, clindamycin 450 mg orally 4x/d **or** metronidazole 500 mg bid + doxycycline can be used for continued therapy rather than doxycycline alone; this regimen provides more effective anaerobic coverage
Regimen B	Clindamycin 900 mg IV q 8 h + gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by maintenance dose (1.5 mg/kg) q 8 h (Single daily dosing of gentamicin 3–5 mg/kg may be substituted)	• Parenteral therapy may be discontinued 24 h after evidence of clinical improvement • Oral therapy with doxycycline 100 mg bid or clindamycin 450 mg po 4x/d should continue through completion of a total of 14 d of therapy • When tubo-ovarian abscess is present, clindamycin should be continued, rather than doxycycline, to provide more effective anaerobic coverage

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1; see same for alternative oral and parenteral regimens

6

Oral Regimens

- Ceftriaxone 250 mg IM in a single dose + doxycycline 100 mg po bid x 14 days +/- metronidazole 500 mg po bid x 14 days, **or**

- Cefoxitin 2 g IM in a single dose + probenecid 1 g po administered concurrently in a single dose + doxycycline 100 mg po bid x 14 days +/- metronidazole 500 mg po bid x 14 days, **or**

- Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) + doxycycline 100 mg po bid x 14 days +/- metronidazole 500 mg po bid x 14 days

Sexual partners of women diagnosed with PID should be evaluated and treated presumptively for gonorrhea and chlamydia if the couple have had sexual contact within the 60 days preceding the onset of symptoms.

Other Causes of Pelvic and/or Lower Abdominal Pain

Ruptured/hemorrhagic ovarian cyst: A ruptured cyst can cause acute pelvic/abdominal pain. Bleeding associated with rupture is usually self-limited but may require surgical intervention.

Ovarian torsion: Torsion can cause acute, severe, unilateral lower-abdominal/pelvic pain, often with a history of previous similar episodes. A palpable adnexal mass is often present. Surgical intervention is required.

Uterine leiomyomas (fibroids): Fibroids may cause pain with rapid enlargement, degeneration, or torsion. Referral to a gynecologic specialist is indicated for management.

Endometriosis: This condition can cause acute or chronic pain and usually includes secondary dysmenorrhea and/or dyspareunia. Referral to a gynecologic specialist is indicated if endometriosis is suspected.

Dysmenorrhea: This cyclic pain with menses affects about 50% of all menstruating women. Primary dysmenorrhea is menstrual pain in the absence of pelvic pathology; secondary dysmenorrhea is associated with underlying pathology, such as endometriosis. Treatment of primary dysmenorrhea consists of nonsteroidal anti-inflammatory drugs (NSAIDs), which are 80% effective, or oral contraceptive pills, which are 90% effective. Treatment of secondary dysmenorrhea is directed at the specific underlying problem.

Mittelschmerz: This pain with ovulation is generally self-limited and is managed with NSAIDs.

Gastrointestinal pathology: Opportunistic infections, including cryptosporidia, CMV, and *M. avium* may cause chronic diarrhea in patients with AIDS; clinical features usually include abdominal pain. Other types of GI pathology include

- appendicitis;
- diverticulitis, with pain generally localized to the left lower quadrant (usually seen at older ages);
- irritable bowel syndrome, in which pain is usually intermittent, cramp-like, more common in the left lower quadrant, and exacerbated by certain foods;
- inflammatory bowel disease;
- infectious enterocolitis, with pain, cramping, and diarrhea; and
- obstruction, with colicky pain, distention, vomiting, and obstipation.

Urinary tract pathology: Pathology of the urinary tract may include renal and/or ureteral stones, cystitis, and pyelonephritis. Urinalysis and urine culture should identify the presence of infection, which should be treated on the basis of microbial sensitivities. Renal or ureteral stones are generally associated with severe, often colicky pain and hematuria; ultrasound or other imaging of the urinary tract may show partial obstruction. The patient generally needs IV fluids, pain control, and possibly lithotripsy. Referral to a urologic specialist is indicated.

Medication-related pathology: Indinavir may cause renal stones; didanosine may cause pancreatitis.

Pelvic Mass

A pelvic mass may be detected by the patient or may be felt on abdominal or pelvic exam. Symptoms vary; a mass often may occur without any symptoms.

History, Physical Exam, Evaluation, and Differential Diagnosis

History

- Presence and duration of associated symptoms
- Pain
- Abnormal vaginal bleeding or discharge
- Urinary symptoms (e.g., frequency, urinary retention)
- Gastrointestinal symptoms (e.g., nausea, vomiting, constipation, diarrhea, bloating)
- Constitutional symptoms (e.g., fever, chills, sweats, weight loss or gain)

Physical Exam

- Vital signs
- Constitutional signs
- Complete abdominal and pelvic examination, with particular attention given to
  - Size, location, mobility, and characteristics of the mass if palpable
    - ° With functional ovarian cysts, a normal ovary may be up to 5 cm–6 cm in size for a woman in the reproductive age range
    - ° A palpable ovary in a postmenopausal woman may be abnormal and requires further evaluation
- Signs of ascites
- Lymph node survey

Evaluation

- Pregnancy test if premenopausal
- Laboratory tests
  - CBC with differential
  - chemistry panel
  - tumor markers if indicated (e.g., carcino-embryonic antigen, Ca-125; tests for these markers produce frequent false positives and false negatives and should be used only in conjunction with other diagnostic procedures)
- Radiologic studies as indicated
  - pelvic ultrasound (transabdominal and/or transvaginal): generally the first diagnostic modality employed in evaluating pelvic anatomy; concerning characteristics include a complex or solid mass and the presence of ascites
  - CT and/or MRI: if indicated; CT and/or MRI are better than ultrasound at imaging the GI tract, retroperitoneal lymphadenopathy, and liver
- Additional evaluation (e.g., laparoscopy, colonoscopy): refer to appropriate specialists

Differential Diagnosis

- **Ectopic pregnancy:** primary consideration in the setting of an adnexal mass and a positive pregnancy test; urgent evaluation is indicated
- **Ovarian functional cysts:** most-common ovarian masses found among women of reproductive age; usually less than 5 cm–6 cm in size; resolution occurs spontaneously in 1–3 months
- **Uterine leiomyomas (fibroids):** often asymptomatic, but may be associated with heavy and/or prolonged menses, urinary frequency, or sensation of pelvic pressure
- **Endometrioma:** consider in women with a documented or suspected history of endometriosis
- **Hydrosalpinx/pyosalpinx and tubo-ovarian abscess:** consider in women with a history and exam suggestive of PID; initial management is with broad-spectrum antibiotics, even if the patient is asymptomatic
- **Benign or malignant ovarian neoplasm:** surgical intervention required
  - no evidence of increased prevalence in HIV infected women, although anecdotal reports suggest ovarian cancer may present at a more advanced stage, with a poorer response to cytoreductive surgery and chemotherapy (*Obstet Gynecol Surv* 1996;51:679)
  - non-Hodgkin's lymphoma of the ovary in an HIV infected woman has been described (*Obstet Gynecol* 1996;88:706)
- **Retroperitoneal lymphadenopathy:** may present as a pelvic mass; possible causes include tuberculosis, lymphoma
- **Gastrointestinal masses:** includes diverticular abscess and bowel malignancy

Note: In general, the presence of a pelvic or abdominal mass requires expert consultation and referral to an appropriate specialist.

Urinary Symptoms

Urinary symptoms are common complaints in both HIV infected and uninfected women. Causes of symptoms include both lower and upper urinary tract disease.

History, Physical Exam, Evaluation, and Differential Diagnosis and Management

History

- Duration and severity of urinary symptoms:
  - dysuria
  - pain with urination
  - frequency
  - urgency
  - hematuria
  - nocturia
  - incontinence
- Associated symptoms:
  - pain, suprapubic or flank
  - fever
  - chills
  - weight loss
- Other medical conditions (e.g., diabetes, sickle-cell disease)

- Surgical history
- Medications (increased risk of renal toxicity with TDF, IDV, ATV)
- CD4+ cell count and VL

Physical Exam

- Vital signs
- Abdominal exam: document presence of suprapubic, flank, or costovertebral angle tenderness
- Pelvic exam: document presence of vulvar sores/ulcers, vaginal atrophic changes or discharge, palpable pelvic mass or tenderness

Evaluation

- Microscopic exam of urine (midstream, clean-catch urinalysis) or catheterized specimen (contamination from vaginal discharge or bleeding may occur if a simple voided specimen is collected)
- Urine culture and sensitivity
- Gonorrhea and chlamydia testing, if indicated
- Urine cytology: consider in women aged >50 y who present with irritative symptoms or hematuria and negative culture
- Urine for acid-fast bacillus (AFB) culture; purified protein derivative (PPD) or interferon gamma release assay, if urinary TB is suspected
- Urinary tract imaging (if indicated; consider if stones, urinary tract anomalies, or urinary TB is suspected)
  - CT
  - ultrasound
  - intravenous pyelogram
- Other tests: cystoscopy, urodynamics—refer to appropriate specialist

Differential Diagnosis and Management

- **Bacterial urinary tract infection:** lower tract (cystitis) or upper tract (pyelonephritis); may be asymptomatic; clinical signs and symptoms cannot reliably distinguish between upper- and lower-tract infection
  - **Cystitis** is classically characterized by the presence of dull, suprapubic pain. Typical associated symptoms include dysuria, urinary frequency and urgency, and occasionally hematuria.
    ° *Vulvar dysuria* is the sensation of burning when urine flows over the vulva and can be misdiagnosed as a urinary tract infection; it is often caused by active herpetic or other vulvar lesions
  - **Pyelonephritis** is associated with flank or costovertebral pain and tenderness to percussion. Typical systemic signs and symptoms include fever, chills, nausea, vomiting, and tachycardia. Treat with appropriate antibiotics; severe pyelonephritis requires hospitalization for IV antibiotics and hydration.
- **Urethral syndrome:** dysuria, frequency with negative urine culture
  - Rule out urethritis due to gonorrheal or chlamydial infection
- **Renal and/or ureteral stones:** characterized by severe, colicky pain
  - Stones are usually associated with urinary stasis or chronic infection, although they may be related to metabolic abnormalities such as gout or to problems with calcium homeostasis
  - Atazanavir and indinavir therapy increase the risk for stones
  - IV hydration and pain control are often required; surgical intervention is sometimes needed
- **Interstitial cystitis:** symptoms include severe urinary frequency and urgency (urinating as often as every 15 minutes daytime and nighttime) as well as suprapubic or perineal discomfort before, during, and after urination
  - Refer to a urologic specialist for definitive evaluation

- **Urinary tuberculosis:** one of the most common sites of extrapulmonary TB
  - Consider with gross or microscopic hematuria and pyuria with negative bacterial culture; manage with expert consultation
- **Tumors:** most common presenting complaint is gross or microscopic hematuria; hematuria without identifiable etiology (e.g., infection) requires referral to a urologist
- **Urinary incontinence:** can be caused by many factors, including anatomic displacements related to aging and childbearing; bladder muscle (detrusor) instability; neurologic disease; infection; fistulas secondary to surgical injury, radiation, or cancer; and some medications
  - Review medication list
  - Rule out infection with culture and "overflow" incontinence secondary to an overdistended bladder with postvoid catheterization for residual urine determination
  - Further evaluation requires referral to a urogynecologist or urologist
  - Management depends on etiology and is beyond the scope of this manual; expert consultation is recommended
- **Urinary retention:** may be caused by obstruction, neurologic disorders, or certain medications (e.g., antihistamines, antidepressants, antipsychotics, opiates, antispasmodics, terbutaline, over-the-counter cold remedies)
- **HIV-associated nephropathy:** presents with nephrotic syndrome and progressive renal failure; may have symptoms of increased urination, excessive thirst, and fatigue
  - If untreated, may lead to end-stage renal disease
  - Risk is increased in African Americans and injection drug users
  - Usually occurs with advanced disease and, generally, CD4+ cell count <200 cells/mm^3

Genital Warts

Genital warts are a common manifestation of HPV infection. HPV types 6 and 11 are usually the cause of visible genital warts. Oncogenic types (i.e., 16, 18, 31, 33, and 35) are occasionally found in visible warts and have been associated with squamous intraepithelial neoplasia of the external genitalia (see **Abnormal Pap Smear**, p. 160).

HIV infected women are more likely to have HPV co-infection, and both the prevalence and incidence of genital warts are greater in infected than uninfected women. Increased immunosuppression is associated with an increased prevalence and incidence of warts, larger or more numerous warts, poorer response to therapy for genital warts, and more frequent recurrences after treatment (*Sex Transm Dis* 2002;29:427; *Sex Transm Dis* 2002;29:121; *Lancet* 2002;359(9301):108; *AIDS* 2008;22:1213). ART and immune reconstitution have been associated with a decreased incidence of warts after treatment (*Am J Obstet Gynecol* 2004;190:1241). Squamous cell carcinomas that arise in or resemble genital warts may occur more commonly in the setting of immunosuppression, making confirmation of the diagnosis with biopsy more often necessary.

History, Physical Exam, and Evaluation

History

- Location of warts
- Duration
- Presence of associated symptoms (e.g., itching, irritation, pain, bleeding)
- History of prior occurrences of similar lesions and their treatment
- History of abnormal Pap smear results

Physical Exam

- Perform a complete examination of the external genitalia, vagina, cervix, and perianal region. Increasingly, HPV disease is found in the oral cavity, which should be examined as well.
- Document the location, size, and characteristics of warts
  - Genital warts can present as cauliflower-shaped growths (condyloma acuminata); smooth, dome-shaped, skin-colored papules; keratotic warts with a thick horny layer; or flat or slightly raised flat-topped papules

Evaluation

- **Biopsy:** Biopsy of the lesion and histopathologic confirmation of the diagnosis are always indicated in the following situations:
  - Diagnosis is uncertain
  - Warts do not respond to therapy
  - Lesions worsen during therapy
  - Warts are pigmented, indurated, fixed, or ulcerated
- Typical condyloma acuminata are diagnosed by inspection and do not require biopsy, although current CDC guidelines suggest biopsy when the patient is immunocompromised
- **Colposcopy:** Colposcopy and directed biopsies of the entire lower genital tract should be considered in HIV infected women with evidence of HPV infection
  - Perform colposcopy and biopsy to rule out the presence of HSIL before initiating treatment of cervical warts

Treatment: The primary goal of treatment is the removal of symptomatic lesions. When left untreated, visible warts may resolve spontaneously, may remain unchanged, or may increase in number or size. There is no evidence that currently available therapies eradicate HPV, affect the natural history of infection, or affect the subsequent development of cervical cancer. Infectivity may or may not be decreased by the removal of visible warts.

The choice of treatment modality depends on the number, size, and location of warts. When the lesions are few in number and fairly small in size, a topical agent may be employed. Table 6-8 presents provider-applied and patient-administered regimens recommended by the CDC (*MMWR Recomm Rep* 2010;59(RR-12):1). Intralesional interferon is an alternative to the therapies listed below, but it is expensive and associated with a high frequency of systemic side effects. Efficacy data are limited for the two other alternatives, photodynamic therapy and topical cidofovir.

Most treatment modalities are associated with mild to moderate discomfort and local irritation. Persistent hypo- or hyperpigmentation is common after ablative therapies and can occur with imiquimod. Rarely, scarring or chronic pain can occur at the treatment site. Warts located on moist surfaces respond best to topical treatment.

Most genital warts respond within 3 months of therapy. The treatment method should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. Data are limited on combining modalities, which does not necessarily increase efficacy but may increase complications.

Recurrence rates are significant with all modalities; frequent follow-up will allow retreatment when new warts are small and few in number. When the number of warts is large or the lesions are very extensive, consider referral for possible laser or excisional surgery.

Table 6-8

Recommended Management of Genital Warts

Provider-applied	Patient-applied
TCA or BCA: • Weekly application if necessary • Remove excess acid with talc powder, baking soda, or liquid soap	**Podofilox 0.5% solution or gel:** • Apply bid x 3 d, then 4 d of no therapy • May repeat application for up to four cycles • Should be limited to 0.5 mL/d and <10 cm^2 area of warts • Avoid during pregnancy
Cryotherapy with liquid nitrogen or cryoprobe: • Repeat every 1–2 wk	**Imiquimod 5% cream:** • Apply 3x/wk for up to 16 wk • Treated area should be washed with mild soap and water 6–10 h after application • Avoid during pregnancy
Podophyllin resin 10%–25%: • Weekly application if necessary • Limit application to <0.5 mL of podophyllin or <10 cm^2 of warts per session • Preparation should be thoroughly washed off 1–4 h after application to reduce local irritation • Avoid use on mucosal surfaces or with any open wounds or lesions because of concern about potential systemic absorption and toxicity • Avoid during pregnancy	**Sinecatechins 15% ointment:** • Apply tid (0.5 cm strand of ointment to each wart) • Do not continue past 16 wk • Do not wash off after use • Avoid sexual contact while ointment is on skin • Not currently recommended for HIV infected women because of lack of safety/efficacy data in HIV setting • Avoid during pregnancy
Surgical removal: Laser or excision	

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

Genital Masses and/or Nodules

Genital masses or nodules are relatively common complaints among women in general and may be associated with pain or discomfort or with no symptoms at all. All genital masses or nodules, however, require careful evaluation for appropriate diagnosis and management.

History, Physical Exam, Evaluation, and Differential Diagnosis and Management

History

- Duration
- Changes in size or appearance
- Associated symptoms (e.g., pain, tenderness, itching, edema)
- History of similar nodules and their treatment
- Sexual history, including the presence of similar lesions on partner's genitals
- Medications
- CD4+ cell count and VL

Physical Exam

- Document anatomic location, number, and size of nodules
- Presence of associated edema, erythema, induration, fluctuance, tenderness, discharge, or bleeding

Evaluation

- Biopsy indicated if etiology is unclear
- Culture abscess contents

Differential Diagnosis and Management (*JAMA* 2003;290:1001)

- Bartholin's abscess or cyst
- Genital warts (see p. 198)
- *Molluscum contagiosum*
- Subepithelial cysts, folliculitis
- Tumors, other masses

Bartholin's Abscess or Cyst

Bartholin's glands are normally nonpalpable and located deep in the perineum at the 5 o'clock and 7 o'clock positions in the entrance to the vagina. Obstruction of a Bartholin's duct by nonspecific inflammation, infection (e.g., gonorrhea or chlamydia), or trauma can lead to the formation of an exquisitely tender abscess. Treatment consists of incision and drainage. Often a residual Bartholin cyst is present after the resolution of infection. This does not require treatment unless it becomes repeatedly infected, is growing, or is otherwise symptomatic. The differential diagnosis of a new-onset mass in the Bartholin's region in women aged >40 years must include malignancy.

Molluscum contagiosum

Molluscum contagiosum is an asymptomatic viral disease that primarily affects the skin of the vulva, although in immunosuppressed patients it can present as a generalized skin disease. It is spread through sexual and nonsexual close contact. Clinical presentation is small nodules or domed papules, usually 1 mm–5 mm in diameter; more mature nodules appear to have an umbilicated center. This disease tends to be self-limited; however, the disease course may be complicated by repeat infection and autoinoculation of the virus.

***Molluscum contagiosum* in HIV infected patients:** This disease affects 5%–10% of HIV infected patients. Extensive, severe lesions that respond poorly to therapy are common, particularly with more advanced immunosuppression. Unresponsive lesions have been found to regress with ART (*Indian J Dermatol* 2009;54(2):180; *Eur J Dermatol* 1999;9:211), but they have also been reported as a manifestation of immune reconstitution syndrome (*Dermatol Online J* 2007;13(2):6).

Treatment: Treatment consists of serial applications of liquid nitrogen or removal of nodules with a dermal curet and chemical cauterization of the base with 85% trichloroacetic acid or ferric subsulfate. Successful eradication with systemic interferon has been reported in an immunocompromised patient (*Dermatology* 2008;217(3):196).

Cysts and Folliculitis

Several benign processes in the genital area may present as a mass or nodule and are self-limited, requiring no or limited specific treatment. These are generally small and minimally symptomatic and can usually be diagnosed on the basis of typical appearance.

Tumors and Other Masses

A biopsy is required for suspected tumors and other masses; expert consultation is indicated.

Genital Itching and/or Irritation

Genital itching and irritation are among the most common gynecologic complaints in both HIV infected and uninfected women.

History, Physical Exam, Evaluation, and Differential Diagnosis and Management

History

- Duration, location, and severity of pruritus/irritation
- Associated symptoms (e.g., erythema, edema, vulvar burning, dysuria, dyspareunia, vaginal discharge)
- Prior episodes of similar symptoms and treatment
- Exposure to particular agents coincident with onset of symptoms (see **Allergic and/or Irritative Reaction**, p. 204)
- Presence of similar symptoms or a recent diagnosis of genital tract infection in close contacts
- Medications, including antibiotics
- CD4+ cell count
- HIV VL

Physical Exam

- Physical appearance and distribution of any lesions on irritated area (e.g., diffuse rash, papular or vesicular lesions, skin burrows)
- Associated findings, including erythema, edema, tenderness, or vaginal discharge
- More thorough inspection of the skin over the whole body may be indicated if a more generalized process is suspected (e.g., scabies, allergic reaction to detergent)

Evaluation

- Fungal culture and/or KOH preparation is indicated if fungal infection is suspected
- HSV culture: herpes may appear atypically and should be ruled out in the presence of vesicular lesions, unexplained abrasions, fissuring, or if warranted by history
- Other cultures/saline wet mount, if indicated by exam findings
- Skin scrapings: the skin papule is scraped with a needle and the crust is placed under a drop of mineral oil on a slide; eggs, parasites, or fecal pellets microscopically visualized by this technique are diagnostic of scabies or pubic lice. A biopsy should be considered if other diagnostic tests are negative or with lack of response to treatment.

Differential Diagnosis and Management (*JAMA* 2003;290:1001)

- Fungal infection
- Allergic and/or irritative reaction
- Scabies
- Pediculosis pubis
- Other: vaginitis or cervicitis, vulvar atrophic changes, vulvar dystrophy

Fungal Infection

Although the primary symptom associated with fungal infections is itching, women also complain of vulvar burning, dysuria, and dyspareunia, particularly with the involvement of vulvar skin. Examination often reveals edema, erythema, and excoriation; when extensive skin involvement is present, pustular lesions may be found to extend beyond the line of erythema.

Diagnosis: Fungal infection is diagnosed through KOH preparation or fungal culture.

Treatment: The infection is treated with the topical application of an antifungal preparation (see **Vulvovaginal Candidiasis**, p. 182).

Allergic and/or Irritative Reaction

Contact dermatitis frequently affects the vulvar skin, particularly the intertriginous areas. Etiologic agents include urine or feces, latex, semen, and cosmetic or therapeutic agents, including vaginal contraceptives, lubricants, sprays, perfumes, douches, fabric dyes, fabric softeners, synthetic fibers, bleaches, soaps, chlorine, dyes in toilet tissues, and local anesthetic creams. Severe cases of dermatitis may be due to poison ivy or poison oak. Typical symptoms are itching, vulvar burning, and tenderness.

Diagnosis: Examination of the skin reveals erythema, edema, and inflammation; the skin may be weeping and eczematoid. Secondary infection may occur.

Treatment: Remove the offending agent. Severe lesions may be treated with wet compresses of Burow's solution diluted 1:20 for 30 minutes several times a day. If possible, the vulva should be dried with cool air from a hair dryer following application of the compresses. Lubricating agents such as Eucerin cream or petroleum jelly can help reduce the itching. Nonmedicated baby powders can be used to facilitate vulvar dryness. Symptomatic relief can be achieved with hydrocortisone (0.5%–1%) or fluorinated corticosteroid (Valisone 0.1% or Synalar 0.01%) lotions or creams applied to the skin two to three times a day for a few days. Dermatitis due to poison ivy or poison oak may require treatment with systemic corticosteroids. The use of white cotton undergarments is advisable, and tight-fitting clothing should be avoided.

Scabies

Scabies is a parasitic infection produced by the itch mite *Sarcoptes scabiei*. It is sexually acquired in adults. The main reported symptom is severe, intermittent itching that tends to be more intense at night.

Diagnosis: Lesions can present as vesicles, papules, or burrows; although any area of skin may be affected, hands, wrists, breasts, vulva, and buttocks are most often affected. HIV infected and other immunosuppressed patients are at increased risk for crusted or Norwegian scabies, a disseminated dermatologic infection, which can appear classically as hyperkeratotic, nonpruritic lesions; as crusting with pruritus; as a pruritic, papular dermatitis; or as lesions resembling psoriasis (*South Med J* 1994;87:352).

Treatment: The CDC-recommended treatment for scabies is permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8–14 hours **or** ivermectin 200 mcg/kg po, repeated in 2 weeks (*MMWR Recomm Rep* 2010;59(RR-12):1). An alternative regimen is lindane (1%) 1 oz of lotion or 30 g of cream applied to all areas of the body from the neck down and washed off thoroughly after 8 hours. Lindane should not be used by pregnant or lactating women and should not be used after a bath.

Itching may persist for days following treatment; antihistamine therapy should be considered for symptomatic relief. Bedding and clothing should be decontaminated (machine washed or dry cleaned) or removed from body contact for at least 72 hours. Norwegian scabies should be managed in consultation with an expert.

Pediculosis Pubis

Pediculosis pubis is caused by infestation with the crab louse *Phthirus pubis*, or pubic louse. Transmission is by close contact, but the louse can also be acquired from bedding or towels. This infection is usually confined to the hairy areas of the vulva, although eyelids are occasionally infested. The presenting symptom is constant itching in the pubic area.

Diagnosis: Eggs, adult lice, and fecal material can be seen upon close examination, without magnification. The diagnosis can be definitively established by microscopic visualization, as described above.

Treatment: The CDC-recommended treatment is permethrin 1% cream rinse *or* pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 minutes (*MMWR Recomm Rep* 2010;59(RR-12):1). Alternative regimens include malathion 0.5% lotion applied for 8–12 hours and then washed off *or* ivermectin 250 mcg/kg orally, repeated in 2 weeks if symptoms do not resolve.

Patients should be reexamined in 1 week; re-treat if lice or eggs are seen at the hair–skin junction. All clothing and bedding must be decontaminated (i.e., either dry cleaned or machine washed and dried using the hot setting) or removed from body contact for at least 72 hours. Close household contacts and recent sexual contacts (i.e., within the previous month) should be treated.

Other: Vaginitis or Cervicitis, Vulvar Atrophic Changes, Vulvar Dystrophy

Diagnosis: based on exam findings and the results of cultures and/or saline wet mount when indicated. A biopsy may be needed if lesions are seen (scaly, hypertrophic, fissures).

Treatment: indicated if another infectious process is identified; topical estrogen for atrophic vaginitis and/or vulvitis; topical steroid therapy empirically for suspected vulvar dystrophy or other dermatosis, with biopsy if symptoms or lesions do not resolve.

6

Breast Lump

A clinical breast exam should be part of the routine physical examination for all HIV infected women and should be performed on an at least an annual basis. The presence of a breast lump always requires further evaluation, depending on the factors listed below.

History, Physical Exam, Evaluation, and Differential Diagnosis and Management

History

- Palpable by the patient?
- Duration of lump
- Any associated symptoms (e.g., tenderness, nipple discharge or bleeding, cyclic pain)
- Changes in characteristics of the lump (e.g., increase in size)
- Menstrual phase or menopausal status
- History of previous breast lumps
- Family history of breast disease, cancer, or history of genetic screening showing BRCA-1 or BRCA-2 mutation
- Mammogram history

Physical Exam

- Examination of both breasts: symmetry, contour, and general appearance of the breasts; presence of edema, erythema, skin dimpling, or nipple retraction
- Presence and size of dominant masses; nodularity, tenderness, mobility
- Nipple discharge, including color; evidence of blood
- Lymph node survey: lymphadenopathy, axillary and supraclavicular

Evaluation

- Mammogram should be performed with any persistent palpable mass or other suspicious changes in the breast (e.g., bloody nipple discharge, skin retraction)
  - Negative mammogram alone is not sufficient to rule out malignant pathology in a patient with a palpable breast mass or bloody nipple discharge; further evaluation and a possible biopsy are indicated
- Ultrasound is most helpful to distinguish cystic and solid masses
  - Useful initial test in younger women when a simple cyst is suspected
- Needle aspiration for cystic lesion
  - Fluid can be discarded if clear and if mass disappears
  - Otherwise, send fluid for cytology; biopsy may be needed
- Biopsy is indicated in cases of a dominant mass, even with normal mammographic findings, or suspicious nonpalpable mammographic findings

Differential Diagnosis and Management

- Fibrocystic changes
- Fat maldistribution syndrome
- Breast abscess and/or mastitis
- Benign breast tumor
- Breast cancer

Fibrocystic Changes

Fibrocystic changes are typically found among women aged 30–50 years.

Diagnosis: Fibrocystic changes usually present as breast nodularity associated with cyclic bilateral pain or tenderness that is worse premenstrually. Breast engorgement, increased density, and cyst formation are common and vary with the menstrual-cycle phase.

Treatment: The pain/discomfort associated with this condition can be relieved by wearing a brassiere that gives adequate support. Analgesics can aid in symptomatic relief. Some women have reported improvement of symptoms with vitamin E (400 IU per day) and a decrease in caffeine consumption. Oral contraceptives are known to decrease benign breast disease. The appearance of a persistent dominant mass requires a biopsy.

Fat Maldistribution Syndrome

HIV or antiretroviral treatment may affect breast tissue, resulting in gynecomastia or increased fatty deposition (*Breast J* 2002;8:234).

Breast Abscess and/or Mastitis

This condition usually presents with tender breasts with evidence of inflammation (redness, swelling). If an abscess is present, a fluctuant mass may be palpated; fever may be present. The etiology is generally bacterial, but tuberculous mastitis and/or abscess should be considered in appropriate circumstances. This condition is most commonly, but not exclusively, seen in lactating women.

Treatment: Antibiotics, incision and drainage of abscess. Consider a biopsy and/or other diagnostic tests with nonresponse to treatment.

Benign Breast Tumor

The most frequently diagnosed benign tumors of the breast are fibroadenomas, which are usually found in women aged 20–35 years. Typically, masses are about 2 cm–3 cm in diameter, although they can become much larger. Examination reveals a firm, smooth, rubbery mass that is freely mobile. Inflammation, skin dimpling, and nipple retraction are absent. On mammographic examination, the mass appears smooth with well-defined margins.

Diagnosis: Definitive diagnosis is established by means of a biopsy.

Treatment: A fibroadenoma may simply be observed; however, a large, growing, or otherwise suspicious mass should be surgically excised.

Breast Cancer

The incidence of breast cancer increases with age. Risk factors include a positive family history, early menarche, late menopause, and nulliparity or late childbearing. If a palpable mass is present, it is usually firm and nontender, with irregular margins; it may be fixed to skin or underlying tissue.

Diagnosis: Definitive diagnosis is established by means of a needle or open biopsy; referral to a surgeon is indicated.

Breast cancer in HIV infected patients: There is no apparent increase in the incidence of breast cancer among HIV infected women; however, breast cancer in the setting of HIV infection may occur at a relatively early age, may be more likely to be bilateral and to have unusual histology, and may be more aggressive, with early metastatic spread and poor outcome. Most cases occur in women with CD4+ cell counts above 200 cells/mm^3. Kaposi's sarcoma and non-Hodgkin's lymphoma may also be localized to the breast in women with AIDS (*Breast J* 2002;8:234; *Cancer Invest* 2002;20:452).

Sexual Dysfunction

When the validated Female Sexual Function Index (FSFI) was administered to women in the WIHS cohort, HIV infected women reported more sexual problems than uninfected women. Lower sexual function was also associated with menopause, symptoms of depression, or not being in a relationship. Women with CD4+ cell counts <200 cells/mm^3 also reported lower sexual functioning than did women with higher CD4+ cell counts (*J Acquir Immune Defic Syndr* 2010;54(4):360). In another study of the responses of clinically stable women with HIV to the FSFI, one-third reported sexual dysfunction. The major determinant was self-perceived body changes; there were no significant associations with sex hormones, CDC stage, CD4+ cell count, HIV RNA level, or cumulative exposure to ARV drugs (*Antivir Ther* 2009;14(1):85).

Clinicians should proactively address issues related to sexual function and related concerns. Signs and symptoms of menopause (see below) and depression should be assessed and, when indicated, appropriate interventions implemented. Treatment of depression with selective serotonin reuptake inhibitors (SSRIs) is also a common cause of decreased libido or inability to reach orgasm. Because of the possible association with body image and a potential relationship with medication adherence, concerns about changes in body appearance should be addressed when a patient is starting ART and at regular intervals during the course of therapy.

Menopause

Menopause is defined as the permanent cessation of menstruation caused by the loss of ovarian function. The mean age at which women undergo menopause is genetically predetermined; in the United States, the average age of menopause onset is 51–52. As HIV infected women live longer, and as greater numbers of women who are nearing menopause or are postmenopausal become infected, it is increasingly important to consider and address issues related to menopause.

History, Physical Exam, and Evaluation

History

- Last menstrual period
- Recent menstrual pattern (i.e., cycle length, duration, amount of flow)
- Any irregular or intermenstrual bleeding or spotting
- Hot flashes
- Genitourinary dryness/atrophy
- Decreased libido
- Anxiety
- Irritability
- Sleep disturbances
- Depression
- Difficulty with memory
- Urinary symptoms

Physical Exam

- Vagina appears smoother in contour, "drier"
- May be more easily traumatized and more vulnerable to infection

Evaluation

- If indicated, confirmation of menopause can be provided by an elevated serum FSH level and a low estradiol level

Menopause in patients with HIV infection: Although data regarding the effect of HIV on the age at menopause are not conclusive, studies suggest that the mean age at menopause for HIV infected women is 3–4 years younger than that for uninfected women (*J Womens Health* 2007;16:1402). Several factors associated with earlier menopause are common among women with HIV, including smoking, substance abuse, African-American race, lower socioeconomic level, and low relative body weight, and may factor into the earlier onset of menopause (*Menopause Int* 2008;14:163). CD4+ cell count<200 cells/mm³ has also been associated with an earlier onset of menopause (*Clin Infect Dis* 2005;41:1517; *Int J STD AIDS* 2011;22(2):67).

Among women in the WIHS cohort, age at menopause was not affected by HIV status, but amenorrhea lasting longer than 12 months was more common among HIV infected women than among uninfected women. Predictors of ovarian failure included lower BMI and lower serum albumin (*Obstet Gynecol*

2006;108:1423). In a cross-sectional analysis of 429 HIV infected and uninfected women (median age 45 years), HIV infected women on ART had approximately a twofold increase in estradiol levels across the menopause transition, with a potential increased likelihood of abnormal perimenopausal bleeding (*Menopause* 2007;14(5):859).

Women are at increased risk for osteoporosis compared with men, and this risk increases after menopause. Recent studies suggest a potential association between HIV infection, ART, and loss of bone density (*J Acquir Immune Defic Syndr* 2003;33:281). Low bone mineral density has been found to be more prevalent among women with HIV approaching menopause than among uninfected women (*Menopause* 2009;16:199). Results of a population-based case-control study indicated that, even among women with normal bone mineral density, HIV infected women reported significantly more history of fragility fractures than did women in the control group (*Osteoporos Int* 2007;18:1345).

Studies have also found that more than 60% of HIV infected patients are vitamin D insufficient or deficient; in addition to known risk factors, the association of renal insufficiency with the use of some ARV agents is consistent with both HIV-related and treatment-mediated alterations in vitamin D metabolism (*Clin Infect Dis* 2011;52(3):396). Data regarding osteoporosis treatment in HIV infected women are lacking. Nonetheless, standard suggestions can be made for treatment and prevention: increase physical activity, stop smoking, and take calcium and vitamin D supplements. Small studies confirm the benefits and safety of alendronate therapy in HIV infected patients (*AIDS* 2007;21:657).

Management

Hormone replacement therapy (combined estrogen-progestin replacement therapy): Currently, the recommendation is to use HRT to treat menopausal symptoms at the lowest effective dose for the shortest duration needed, with periodic evaluation of the need for continued use.

A variety of estrogen and progestin formulations are available. Estrogen can be given orally, transdermally, or topically; progesterone and/or progestin is generally administered orally or by transdermal patch. These agents can be given on a continuous (daily) basis or cyclically (estrogen given daily and progestin 12–14 days per month). Combined oral and transdermal regimens are available and improve adherence.

The benefits and risks associated with HRT have been studied extensively among HIV uninfected women. HRT is known to ameliorate symptoms of vasomotor instability (e.g., hot flashes, sleep disturbances, irritability) and urogenital atrophy (e.g., vaginal dryness, dyspareunia); it is also associated with a decreased risk of colon cancer, osteoporosis, and osteoporosis-related fractures (*JAMA* 2002;288:321). A recent position paper from the United Kingdom National Osteoporosis Society concluded that HRT has a role to play in the management of osteoporosis in postmenopausal women aged <60 years (*Menopause Int* 2011;17(2):63).

The results of a large, randomized, placebo-controlled study of combined estrogen-progestin therapy (at higher doses than are generally used today and in women with a mean age of 63 years) found a small but statistically significant increase in the incidence of breast cancer, dementia, stroke, pulmonary embolism, and cardiovascular disease (*JAMA* 2002;288:321; *JAMA* 2003;289:2717; *JAMA* 2003;289:3243). An increased risk of endometrial cancer was seen in women treated with estrogen only, which is not recommended for women who still have a uterus.

Because of the higher prevalence of active liver disease in patients co-infected with HIV and hepatitis B or C and a potential increased risk for cardiovascular disease associated with the metabolic changes that occur with long-term ART, HRT may be associated with increased risk in the setting of HIV infection and should be used only if the benefit is felt to outweigh the risk.

Alternatives to Hormone Replacement Therapy

- Progestin-only regimens (medroxyprogesterone acetate 10–30 mg qd or norethindrone 1–5 mg qd) may help relieve hot flashes; the health effects of long-term therapy are unknown

- SSRIs may help relieve hot flashes

- Nonhormonal lubricants and/or moisturizers or local/topical estrogen formulations may be used to manage urogenital atrophy

- Bisphosphonates (e.g., alendronate, ibandronate) may be used for the prevention or treatment of osteoporosis

- Selective estrogen receptor modulators (raloxifene 60 mg po daily) offer bone benefit without evidence of breast or endometrial stimulation. They are also FDA indicated for breast cancer prophylaxis in high-risk postmenopausal women. These drugs have no effect on hot flashes, pose a small increased risk of venous thromboembolism (VTE), and are contraindicated in women with a history of VTE.

6

Health Maintenance Issues

Regardless of coexisting medical problems and even in the absence of gynecologic symptoms, regular gynecologic evaluation and other recommended health screening tests are important to identify potential problems that require further evaluation and treatment.

Gynecologic Evaluation

Perform annually and as indicated by the presence of symptoms, need for follow-up of ongoing problems, exposure to STIs, development of abnormal Pap smear, or other need for referral based on primary care evaluation.

Pap Smears

Perform twice within the first year of HIV diagnosis and then annually. More-frequent screening may be indicated with a history of abnormal Pap smear, HPV infection, and/or after treatment for cervical dysplasia.

Screening for Sexually Transmitted Infections

- Screen annually for syphilis and if neurologic signs and symptoms develop
- Screen annually for gonorrhea, chlamydia, and trichomoniasis in sexually active women. Screen as indicated by the presence of relevant symptoms or exam findings and with a recent change in sexual partners and/or a history of STI in the sexual partner. Screen periodically as indicated by sexual practices (e.g., commercial sex work, multiple sex partners, inconsistent use of condoms) or on patient request.

Mammography

ACOG recommends baseline mammography beginning at age 40 and then every 1–2 years until age 50, with annual screening thereafter (ACOG Committee Opinion No. 483; *Obstet Gynecol* 2011;117(4):1008); women at increased risk (e.g., first-degree relative(s) with breast cancer, BRCA-1 or BRCA-2 mutation) may benefit from earlier initiation of screening or the addition of screening modalities other than mammography, such as ultrasound or MRI. Mammogram should also be performed with the presence of a persistent, palpable mass or other suspicious findings on exam.

Colorectal Cancer Screening

Begin screening at age 50, followed by colonoscopy every 10 years thereafter (preferred). Other screening methods include: 1) annual fecal occult blood testing or fecal immunochemical test (patient-collected; requires 2–3 stool samples collected at home and returned for analysis); 2) flexible sigmoidoscopy every 5 years; 3) double contrast barium enema every 5 years; 4) CT colonography every 5 years; or 5) stool DNA (ACOG Committee Opinion No. 483; *Obstet Gynecol* 2011;117(4):1008).

Begin screening colonoscopy earlier and continue at shorter intervals in women with a family history of colorectal cancer or adenomatous polyps (i.e., in any first-degree relative aged <60 years, or in two or more first-degree relatives at any age), family history of familial polyposis or hereditary nonpolyposis colon cancer, personal history of colorectal cancer, inflammatory bowel disease, or adenomatous polyps. The American College of Gastroenterology recommends that screening in African Americans begin at age 45 with colonoscopy because of increased incidence and earlier age at onset of colorectal cancer (*Am J* Gastroenterol 2005;100:515).

Osteoporosis Prevention

The recommended dietary reference intake for calcium is 1000–2000 mg/day; for vitamin D, 600–800 IU/day (*Dietary Reference Intakes for Calcium and Vitamin D—Consensus Report*. Institute of Medicine. November 2010; http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx. Accessed 7/6/2012). Regular weight-bearing exercise is also recommended. Baseline bone-density screening should be performed at age 65 and periodically thereafter, with the screening interval determined by the presence of bone loss or risk factors for premature bone loss. Earlier screening should be considered in younger postmenopausal women with one or more risk factors for premature bone loss (*Clin Infect Dis* 2009;49(5):651; ACOG Committee Opinion No. 483; *Obstet Gynecol* 2011;117(4):1008).

Risk factors for premature bone loss include
- caucasian or Asian race/ethnicity,
- alcohol abuse,
- smoking,
- low BMI,
- sedentary lifestyle,
- chronic steroid use,
- phenytoin therapy,
- hyperparathyroidism,
- vitamin D deficiency,
- thyroid disease,
- history of prior fracture as an adult,
- dementia,
- family history of osteoporosis,
- premature menopause (<45 years),
- prolonged (>1 year) premenopausal amenorrhea, and
- history of falls.

Vitamin D deficiency is common and is more severe in darker-skinned women; a baseline 25-OH vitamin D level will detect this. Minimal deficiency and levels near the lower limit of normal can be corrected by an over-the-counter vitamin D supplement of 1000 IU daily; more-severe deficiency requires prescription high-dose (50,000 IU) repletion followed by chronic maintenance dosing of 1000 IU/day.

Lipid Screening

Assess and address risk factors for hyperlipidemia at the initial visit and periodically thereafter. Risk factors include a history of cardiovascular, peripheral vascular, or cerebrovascular disease; age >55 years; family history; smoking; diabetes; hypertension; obesity; and physical inactivity. Perform a fasting lipid profile every 6–12 months in all patients and consider performing it 1–3 months after starting or modifying ART (*Clin Infect Dis* 2009;49(5):651).

6

Guidelines for Gynecologic Referral

In general, referral to an obstetric-gynecologic specialist should be considered under the following circumstances:

- Uncertain diagnosis, with a gynecologic condition as part of the differential diagnosis
- Diagnosis of pregnancy
- Inadequate response to standard treatment regimens for gynecologic conditions
- Possible need for surgical intervention
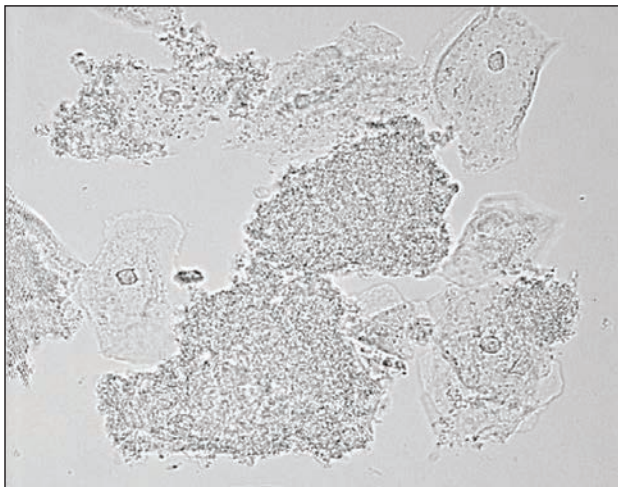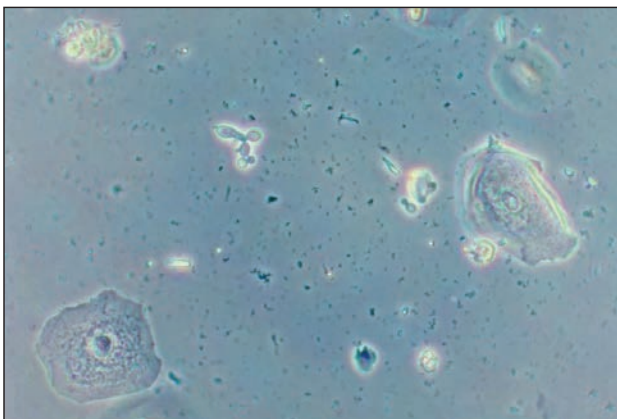- Suspected premalignant or malignant condition

Color Plates

Plate 1.

Trichomonas vaginalis protozoa in a saline wet mount (high power)
(CDC, 1986)

Plate 2.

Clue cells of bacterial vaginosis in saline wet mount (high power)
(Seattle STD/HIV Prevention Training Center at the University of Washington)
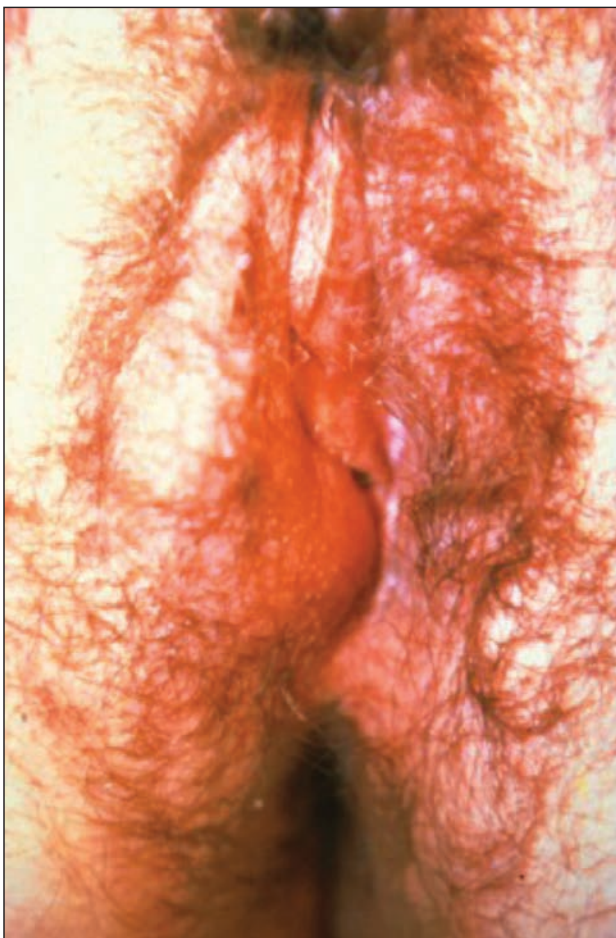
Plate 3.

Candida albicans in a saline wet mount (high power) (CDC/
Dr. Stuart Brown, 1976)

Color Plate 4.
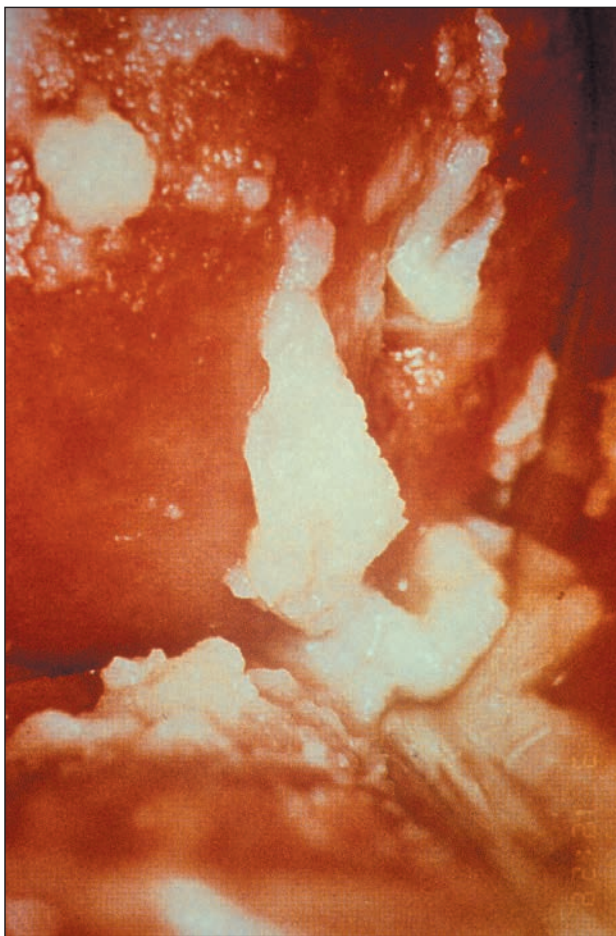
Vaginal candidiasis: thrush patches on the vaginal wall of a patient with candidiasis (© courtesy J. Anderson, MD).

Color Plate 5.

Bartholin's abscess (CDC, Division of STD Prevention)

Color Plate 6.

Chancre in a woman with primary syphilis (CDC, Division of STD Prevention)

Color Plate 7.

Secondary syphilis (CDC, Division of STD Prevention)

Color Plate 8.

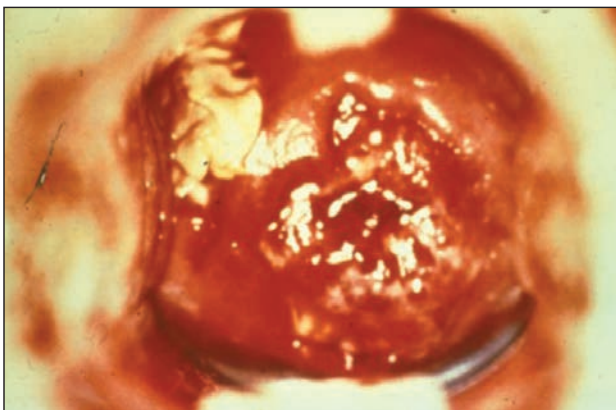Extensive vulvar condylomata acuminata (human papillomavirus) (CDC)
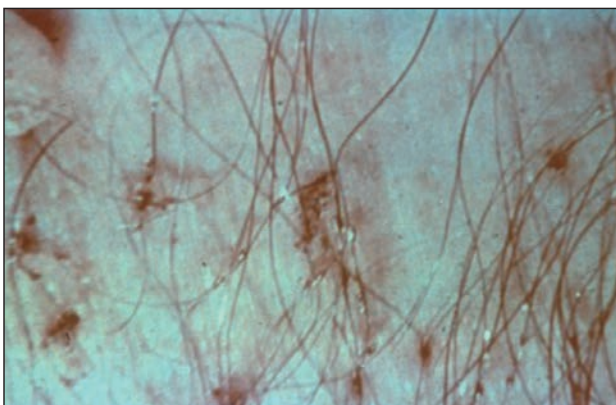
Color Plate 9.

Granuloma inguinale (CDC, Division of STD Prevention)
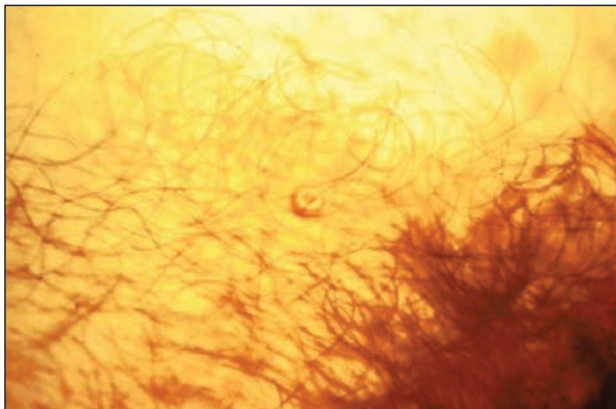
Color Plate 10.

Herpes simplex cervicitis (CDC, Division of STD Prevention)

Color Plate 11.

Lice in pubic area (CDC, Division of STD Prevention)

Color Plate 12.

Molluscum contagiosum (CDC, Division of STD Prevention)

Color Plate 13.

Condylomata late in secondary syphilis (CDC, Division of STD Prevention)

Color Plate 14.

Lesion of herpes simplex (© courtesy J. Anderson, MD).

Color Plate 15.

Herpes simplex in woman with AIDS, CD4<50
(© courtesy J. Anderson, MD).

Color Plate 16.

Aphthous genital ulceration (© courtesy J. Anderson, MD).

Color Plate 17.

Aphthous oral ulceration (© courtesy J. Anderson, MD).