
VI. GYNECOLOGIC PROBLEMS

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I. INTRODUCTION

Gynecologic problems are common among HIV-positive women and are frequently present at the time of initial presentation for evaluation and care. Minkoff et al. found that 46.9% of 262 HIV-infected women had a least one incident gynecologic condition with serial assessment (Minkoff, 1999). In a study of women admitted to an inpatient AIDS service, although only 9% were admitted with a primary gynecologic problem, 83% had coexisting gynecologic disease when evaluated (Frankel, 1997). Some gynecologic issues are unrelated to the patients' 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.

In 1999, women accounted for 23% of the adult AIDS cases and 32% of the adult cases of HIV infection reported in the United States (CDC, 1999). Moreover, women have had the greatest increase in AIDS incidence in recent years when compared with other U.S. population groups. With this background and the fact that HIV infection primarily affects women during their reproductive years, gynecologic and reproductive health care will play an increasingly important role in the overall care of the HIV-infected woman. With improved longevity and quality of life, gynecologic problems will 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.

II. ABNORMAL UTERINE BLEEDING/AMENORRHEA

A. WHAT IS CONSIDERED "ABNORMAL" BLEEDING?

A normal menstrual period should occur every 21 to 35 days and last between 2 and 6 days. The average blood loss during menses is 20 to 60 mL, but up to 14% of healthy women have blood loss greater than 80 mL and are more likely to be anemic because of this (Mishell, 1997a).

Amenorrhea represents a sort of abnormal bleeding in that it is the lack of menstruation. Primary amenorrhea is defined as the absence of menses by age 16. Secondary amenorrhea is the absence of menses for a variable period of time, for at least 3 mo and usually 6 mo or longer, in a woman who has previously menstruated.

B. RELATIONSHIP TO HIV DISEASE

Menstrual disorders are frequently reported by HIV-positive women. However, controlled studies have yielded conflicting evidence regarding whether HIV or HIV-related immunosuppression exerts a clinically significant direct effect on these reported disturbances (Chirgwin, 1996; Ellerbrock, 1996; Shah, 1994) and more definitive studies are needed.

In the setting of HIV infection, menstrual disorders may be related to confounding variables, such as weight loss, chronic disease, substance abuse, and progestational agents used for appetite stimulation or contraception. The impact of antiretroviral therapy on menstruation has not been well studied but hypermenorrhea, or excessive menstrual blood loss, has been reported with zidovudine (Nielsen, 1999). The effect of HIV-RNA levels on menstrual function is unknown.

C. HISTORY

- **Characteristics of bleeding:** date of last normal menstrual period, duration and frequency of menses, amount of bleeding (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.
- **Other bleeding sources:** gastrointestinal (GI) or bleeding from the urinary tract vs. from a gynecologic source); history of easy bruising, nose or gum bleeds.
- **History of gynecologic problems/other symptoms:** abnormal Pap smears; uterine fibroids or polyps; prior ectopic pregnancy; abnormal vaginal discharge.
- **Medical history:** timing of diagnosis of HIV/AIDS and existing comorbid conditions; clinical symptoms of HIV; CD4 count and viral load; history of platelet disorders (thrombocytopenia is frequently diagnosed in HIV infection, particularly in individuals with more advanced stages of disease (Sloand, 1992); medications; history of substance abuse.
- **Sexual history:** last sexual intercourse and use of contraception and condoms.

D. PHYSICAL EXAM

A careful and comprehensive abdominal and pelvic examination should be performed. The presence of abdominal tenderness or mass should be noted. The external genitalia, vagina, and cervix should be inspected for evidence of actively bleeding lesions (e.g., lacerations, condylomata, polyps) or inflammation. Bimanual and rectovaginal examinations assess the presence of pelvic tenderness, enlarged uterus, or other pelvic mass.

E. DIFFERENTIAL DIAGNOSIS

- **Pregnancy.** Pregnancy must be considered in any woman of reproductive age with irregular bleeding or amenorrhea. Pregnancy may be either intrauterine or ectopic (usually tubal); bleeding with an intrauterine pregnancy may indicate threatened or incomplete abortion or miscarriage or a serious obstetric complication in later pregnancy.
- **Anovulation.** Anovulation is the most common cause of abnormal uterine bleeding among reproductive-aged women. Typically, the woman has a history of menstrual irregularity and may go several months with no bleeding, followed by the onset of prolonged and heavy bleeding. Anovulatory bleeding is a diagnosis of exclusion, and organic, systemic, and iatrogenic causes of bleeding must be ruled out. Anovulation and oligoovulation are more common among perimenopausal women and adolescents soon after menarche.
- **Perimenopause.** In addition to anovulation/oligoovulation, women in perimenopause may have irregular menses because of declining estrogen levels.
- **Uterine fibroids.** Fibroids are common benign uterine tumors that are most often asymptomatic, but may cause heavy and/or prolonged periods.
- **Cancer.** Malignant processes in every part of the female genital tract (vulva, vagina, cervix, uterus, fallopian tubes, and ovaries) can potentially present with abnormal bleeding; most common in postmenopausal women.
- **Genital tract infections.** Cervicitis, endometritis, and even vaginitis and vulvitis may present with abnormal vaginal bleeding or spotting. Associated symptoms, including pain/tenderness, discharge, fever, and other signs and symptoms of infection, will aid in making the diagnosis. In very immunosuppressed patients, consider opportunistic processes, including tuberculous or cytomegalovirus (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.** Progestational agents, such as those used for contraception (e.g., Depo-Provera, Norplant) or for appetite stimulation (e.g., Megace) frequently cause irregular vaginal bleeding. 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.

F. EVALUATION

The basic evaluation includes the following:

- **Pregnancy test (urine or serum):** perform on all women with abnormal bleeding/amenorrhea within reproductive age range
- **Laboratory tests:**
 - **Complete blood count (CBC), platelet count**
 - **Thyroid-stimulating hormone, prolactin levels** — consider with any irregular bleeding/amenorrhea without apparent cause
 - **Follicle-stimulating hormone (FSH), estradiol** — with oligomenorrhea/amenorrhea and/or signs/symptoms of decreased estrogen production (hot flashes, vaginal atrophic changes). These tests are particularly helpful in distinguishing ovarian failure (low estradiol, high FSH) and hypothalamic amenorrhea (e.g., with wasting) (low estradiol, low/normal FSH)
 - **Coagulation profile** — if evidence of systemic bleeding, to rule out coagulopathy
- **Cervical testing:** for gonorrhea and chlamydia
- **Pelvic ultrasound:** with abnormal exam (uterine enlargement, adnexal mass, significant tenderness) or positive pregnancy test
- **Endometrial biopsy:** indicated with postmenopausal bleeding, prolonged amenorrhea followed by onset of irregular or heavy bleeding, persistently irregular bleeding. It is helpful in diagnosing endometritis, endometrial hyperplasia, and uterine cancer; endometrial tissue necessary to diagnose CMV or tuberculosis (TB) endometritis—alert your pathologist if these are considerations
- **Pap smear:** do not perform with active bleeding; if cervical lesion seen, biopsy is required.

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

G. MANAGEMENT

Management depends on the diagnosis and results of testing. All women with a positive pregnancy test require referral to a specialist. If anovulatory bleed-

ing is suspected, medical management may be attempted with oral contraceptive pills or cyclic progestins (medroxyprogesterone acetate 10 mg po qd for 10–14 days each month). These therapies help restore regular menstruation, reduce possible anemia, and protect the endometrium from prolonged estrogenic stimulation, which can cause hyperplasia or neoplasia. Oral contraceptive pills will also provide effective contraception, but are contraindicated in heavy smokers over the age of 35, with hypertension or other cardiovascular disease, and in diabetics and women with markedly abnormal liver function.

With severe bleeding and anemia, pelvic mass, findings suspicious for malignancy, or bleeding that is not resolved with conservative measures, referral is indicated.

III. 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 HIV-negative women (Maiman, 1998).

A. INTERRELATIONSHIP OF HIV AND HUMAN PAPILLOMAVIRUS

- Human papillomavirus (HPV) infection plays a causative role in lower genital intraepithelial and invasive neoplasia. The spectrum of HPV disease includes subclinical disease, classic genital warts and other HPV-related skin lesions, lower genital tract intraepithelial neoplasia, and invasive cancers of the lower genital tract. There are over 70 HPV subtypes, which are divided into low, intermediate, or high risk, based on oncogenic potential; nevertheless, these categories are not exclusive and “low-risk” HPV types have been described in cervical carcinomas.
- HPV is an extremely common infection; current evidence suggests that over 50% of sexually active adults have been infected with one or more genital HPV types, but most HPV infections are transient (Evander, 1995; Ho, 1998). Studies have shown that HIV-infected women have higher prevalence of HPV (Minkoff, 1998; Palefsky, 1999; Sha, 1996; Sun, 1997), longer persistence of HPV (Andieh, 2000; Sun, 1997), higher likelihood of multiple HPV subtypes (Brown, 1994), and greater prevalence of oncogenic subtypes (Minkoff, 1998; Uberti-Foppa, 1998) than in HIV-uninfected women.
- In HIV-positive women the prevalence and persistence of HPV infection increases with decreasing CD4 count and increasing HIV RNA levels (Palefsky, 1999) and some studies show that oncogenic HPV types may be more common with lower CD4 counts and/or higher viral loads. (Luque, 1999; Minkoff, 1998).

- Sun et al. (Sun, 1995) have suggested that the presence of immunosuppression shifts the ratio of latent:clinically expressed HPV infections from 8:1 in the general population to 3:1 in HIV-positive women with CD4 > 500/mm³ to 1:1 in HIV-positive women with CD4 < 200/mm³.

B. HIV AND CERVICAL DYSPLASIA

- Abnormal cervical cytology is more common among HIV-infected women and is associated with the presence of HPV infection and the degree of immunosuppression. Both frequency and severity of abnormal Pap smears and histologically documented dysplasia increase with declining CD4 counts and have also been associated with higher HIV-RNA levels (Garzetti, 1995; Shah, 1996). Incidence of abnormal Pap smears is increased with lower CD4 counts (Delmas, 2000).
- In HIV-positive women dysplasia is associated with more extensive cervical involvement and is more likely to involve other sites in the lower genital tract, such as the vagina, vulva, and perianal region (Hillemanns, 1996; Korn, 1995; Maiman, 1990; Petry, 1996; Williams, 1994) as compared with HIV-negative women.
- Recent studies have shown increased incidence of oncogenic HPV types (Minkoff, 1998) and increased incidence of biopsy-proven cervical dysplasia (Ellerbrock, 2000) in HIV-positive women compared with HIV-negative controls. A French study found an increased likelihood of progression of cervical abnormalities in HIV-positive women, although analysis was based on Pap smear results only (Six, 1998). A recent study also found an association between progression of abnormal Pap smears and high plasma HIV RNA levels (>100,000 c/mL)(Sewell, 2000). Presently there is little evidence for increased rates of progression to invasive cancer, particularly if adequate screening and treatment programs are in place.

C. INVASIVE CERVICAL CANCER IN HIV DISEASE

- In 1993, the CDC expanded the case definition of AIDS to include invasive cervical cancer.
- There is little evidence to date that HIV infection is having a significant impact on cervical cancer rates. However, a review of New York City AIDS surveillance data 1990–1995 found that the observed cervical cancer cases were two to three times higher than the expected number of cases (Chiason, 1997a). One study reported a higher prevalence of invasive cervical cancer in HIV-positive compared with HIV-negative hospitalized patients, particularly among those aged 20 to 34 and among African American and Hispanic women (Weber, 1998). In a recent analysis of women in the HER study, HIV-positive women had an invasive cervical cancer rate of 144 per

1,000 person-years as compared with 0 per 1,000 person-years in HIV-negative women (Phelps, 2000). Women with HIV and cervical cancer tend to be younger and less immunosuppressed compared with HIV-positive women with other AIDS-indicator conditions. Women with HIV and cervical cancer tend to be younger than HIV-negative women with cervical cancer (Lomalisa, 2000).

- HIV-positive women with invasive cervical cancer appear to present at more advanced stages (especially with $CD4 < 200/mm^3$), may metastasize to unusual locations (e.g., psoas muscle, clitoris, meningeal involvement), have poorer responses to standard therapy, and have higher recurrences and death rates, as well as shorter intervals to recurrence or death, compared with HIV-negative women of similar stage (Klevens, 1996; Maiman, 1990).

D. SCREENING TESTS

- A single Pap smear is associated with false-negative rates of 10–25%; accuracy is significantly improved with regular periodic screening. Controlled studies have not demonstrated a decrease in sensitivity or specificity with standard cervical cytology in HIV-positive women compared with HIV-negative controls (Adachi, 1993; Spinillo, 1998).
- Newer Pap smear screening techniques using liquid-based media appear to increase sensitivity, decrease inadequate smears, and reduce, but not eliminate, false-negative results; they also offer the possibility of direct HPV testing on collected specimens. They are more expensive than conventional Pap tests; there are no current data examining the utility of these tests in HIV-positive women.
- HPV testing can identify both oncogenic and nononcogenic viral types; such testing may play an important role in the evaluation of women with equivocal Pap smear results (Manos, 1999).
- The role of HPV DNA testing as an alternative or addition to the Pap smear in HIV-positive women is unknown. One small study found that HIV-positive women with normal Pap smears and $CD4$ counts $< 200/mm^3$ and presence of HPV DNA were more likely to have biopsy-proven abnormalities compared with HIV-negative women or HIV-positive women with higher $CD4$ counts (Anderson, 1996b). A recent German study examining HPV DNA testing as a primary screening method for cervical dysplasia in 94 HIV-positive women found that HPV DNA testing identified high-grade cervical dysplasia more accurately than Pap smear (Petry, 1999).
- Pap smear results are reported according to the Bethesda System (National Cancer Institute Workshop, 1989) (Table 6-1).

TABLE 6-1: PAP SMEAR REPORT FORMAT FOR BETHESDA SYSTEM

Statement on specimen adequacy	<ul style="list-style-type: none"> ■ Satisfactory for interpretation ■ Less than optimal ■ Unsatisfactory
General categorization	<ul style="list-style-type: none"> ■ Within normal limits ■ Other/descriptive diagnosis
Descriptive diagnoses	<ul style="list-style-type: none"> ■ Benign cellular changes (including infections) ■ Reactive and reparative cellular changes (including inflammation)
Epithelial cell abnormalities	<ul style="list-style-type: none"> ■ Atypical squamous cells of undetermined significance ■ Low-grade squamous intraepithelial lesion, including HPV changes and mild dysplasia/CIN 1 ■ High-grade squamous intraepithelial lesion, including moderate and severe dysplasia, CIN 2, CIN 3, carcinoma in situ ■ Squamous cell carcinoma ■ Glandular cell abnormalities
Nonepithelial malignant neoplasm	<ul style="list-style-type: none"> ■ Specify
Hormonal evaluation (vaginal smears only)	<ul style="list-style-type: none"> ■ Specify
CIN, cervical intraepithelial neoplasia.	

E. RECOMMENDATIONS FOR PAP SMEAR SCREENING AND COLPOSCOPY

- Both the CDC and the Agency for Health Care Policy and Research recommend that HIV-infected women have a complete gynecologic evaluation, including a Pap smear and pelvic exam, as part of their initial evaluation (CDC, 1998).
- A Pap smear should be obtained twice in the first year after diagnosis of HIV infection. If these results are normal, annual examinations are then indicated.
- More frequent Pap smears should be obtained:
 - with previous abnormal Pap smear
 - with HPV infection
 - after treatment for cervical dysplasia
 - in women with symptomatic HIV infection (including CD4 counts < 200/mm³)
- The American College of Obstetricians and Gynecologists recommends Pap smears every 3–4 mo for the first year after treatment of preinvasive cervical lesions, followed by Pap smears every 6 mo (ACOG, 1993).
- The role of anal cytology is currently under study.
- Indications for colposcopy are outlined in Table 6-2.
- ASCUS (atypical squamous cells of undetermined significance) represents the mildest cytologic abnormality in the Bethesda system; its significance,

TABLE 6-2: INDICATIONS FOR COLPOSCOPY

- Cytologic abnormality (atypia or greater, including ASCUS, AGCUS)
- History of untreated abnormal Pap smear
- Consider periodic colposcopy after treatment of cervical dysplasia
- Consider with evidence of HPV infection
- Consider screening colposcopy with CD4 < 200/mm³

ASCUS, atypical squamous cells of undetermined significance;
 AGCUS, atypical glandular cells of undetermined significance.

TABLE 6-3: SUGGESTED FREQUENCY OF PAP SMEARS

<i>CLINICAL SCENARIO</i>	<i>SCREENING FREQUENCY</i>
Normal Pap	1 yr
Symptomatic infection / CD4 < 200	6 mo
ASCUS/LGSIL (evaluated and followed without treatment)	4–6 mo
Following treatment of preinvasive lesions	3–4 mo for first year, then 6 mo

ASCUS, atypical squamous cells of undetermined significance;
 LGSIL, low-grade squamous intraepithelial lesion.

however, varies tremendously among different cytopathologists and laboratories. Various studies have found underlying dysplasia in 10–60% of women with ASCUS on Pap smear. In a study of women with ASCUS, Wright (Wright, 1996a) found that HIV-positive women were approximately twice as likely to have underlying dysplasia compared with HIV-negative women; a recent cross-sectional analysis of 761 Pap smears from HIV-positive women found that 27% were diagnosed as ASCUS; 15% had underlying high-grade dysplasia (Holcomb, 1999a). Immunosuppression did not appear to increase the frequency of dysplasia associated with ASCUS on Pap smear. In the general population it is recommended that an initial report of ASCUS prompt repeat Pap smear and referral for colposcopy be made with a second ASCUS report. However, given the frequency of cervical abnormalities and the possible increased likelihood of underlying dysplasia with ASCUS in the setting of HIV infection, many experts prefer to proceed with colposcopic evaluation with the initial report of atypical cells. The ability to do this may be limited by availability of colposcopic equipment and trained colposcopists.

- The risk of underlying pathology with a diagnosis of AGCUS (atypical glandular cells of undetermined significance) is significant: 17–34% have associated significant intraepithelial or invasive lesions (Duska, 1998; Kennedy, 1996; Korn, 1998). Colposcopy is indicated with any AGCUS on pap, as well as endocervical and endometrial sampling.
- Biopsies should be obtained at the time of colposcopy to confirm cytologic abnormalities and/or if abnormal areas are visualized.

- Because of the multicentric nature of lower genital tract intraepithelial neoplasia in the setting of immunosuppression, it is recommended that the entire lower genital tract (vagina, vulva, and perianal region) be examined at the time of colposcopy.

F. MANAGEMENT OF CERVICAL LESIONS

Management of abnormal Pap smears is outlined in Table 6-4. Documentation of a high-grade cervical lesion requires treatment. Standard excisional or ablative treatment is recommended, although HIV-positive women have an increased incidence of recurrence after treatment (over 50% recurrence rate), correlated with degree of immunosuppression (Fruchter, 1996; Holcomb, 1999b). Cryotherapy has had the highest rate of recurrences and should be avoided, if other treatment methods are available. Recurrences have been associated with detectable HIV RNA in plasma and higher mean HIV RNA levels (Keller, 2000) and may also be related to positive surgical margins with excisional treatment, which appear to be more common in HIV-positive women compared with HIV-negative women (Boardman, 1999).

Topical vaginal 5-fluorouracil (5-FU) cream (2 g biweekly for 6 mo) was shown to reduce recurrence rates after standard treatment for high-grade cervical dysplasia in HIV-positive women in a recent clinical trial; over 18 mo of follow-up, 31% of women observed only developed a recurrent high-grade lesion compared with 8% of women receiving 5-FU. Disease recurred more slowly in women who had received antiretroviral therapy, compared with those who were antiretroviral-naïve (Maiman, 1999).

5-FU may play a role in secondary prophylaxis of preinvasive cervical lesions in some cases. However, clinical experience with this therapy is too limited to provide a recommendation for routine use. 5-FU may have significant mucosal toxicity and concerns have been raised about the potential for increased risk for transmission of HIV or other sexually transmitted diseases (STDs) with this therapy.

TABLE 6-4: RECOMMENDED MANAGEMENT FOR ABNORMAL PAP SMEARS

<i>PAP SMEAR RESULT</i>	<i>MANAGEMENT (BASED ON HISTOLOGIC FINDINGS)</i>
Severe inflammation	Evaluate for infection; repeat Pap if inadequate
Atypia, atypical squamous cells of undetermined significance	Colposcopy, biopsy if indicated; follow with Pap q 6 mo
Low-grade squamous intraepithelial lesion (CIN 1)	Colposcopy, biopsy if indicated; follow with Pap q 6 mo: consider repeat colposcopy annually
High-grade squamous intraepithelial lesion (CIN 2 or 3, carcinoma in situ)	Colposcopy, biopsy; treat with loop excision or conization
Invasive carcinoma	Colposcopy with biopsy or conization; treat with surgery or radiation (referral to gynecologic oncologist needed)

The role of highly active antiretroviral therapy (HAART) and immune reconstitution in the management of lower genital tract precancerous lesions remains unclear. In one study use of HAART was associated with regression of cervical lesions over a median follow-up of 5 mo (Heard, 1998). However, Duerr and colleagues found no differences in regression of abnormalities on Pap smear, HPV acquisition or persistence after up to 24 mo on HAART compared with untreated women or women receiving non-HAART treatment. However, new abnormal Pap smear results were less likely in the HAART group (Duerr, 2000).

At the current time, HIV-positive women should continue to be followed closely for evidence of lower genital tract neoplasia, regardless of antiretroviral therapy or viral load.

IV. GENITAL ULCERS

A. HISTORY

Duration and location of lesion(s); previous history of genital ulcers, syphilis, or genital herpes; associated symptoms (pain, pruritus, fever, etc.); medications and timing of ulcers relative to initiation of new medication; sexual history (including condom use); and CD4 counts and HIV RNA levels.

B. PHYSICAL EXAM

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.

C. EVALUATION

- Syphilis serology or darkfield examination
- Culture or antigen test for herpes simplex virus (HSV)
- **Biopsy:** with unclear diagnosis, lack of response to treatment; consider special stains, if indicated (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

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

INFECTIONS

Herpes Simplex Virus

- most prevalent infectious cause of genital ulcers in the United States

- two distinct serotypes of HSV (HSV-1 and HSV-2), most cases of recurrent genital herpes (60–95%) are caused by HSV-2
- since the late 1970s, the seroprevalence of HSV-2 infection has increased by 30%; infection is now detectable in 21.9% of people aged 12 or older nationwide (Fleming, 1997)
- typically lesions present as painful vesicles that ulcerate and heal without scarring
- primary infection often associated with systemic symptoms (fever, photophobia, headache); duration of lesions and viral shedding more prolonged with primary infection; after primary episode latency established in sacral dorsal root ganglia
- nonprimary first episode herpes occurs in individuals with antibodies to HSV-2 or HSV-1 but no previous clinical symptoms of HSV; milder, shorter episode
- recurrent episodes occur at variable frequency; more localized lesions, shorter duration compared with first episodes (primary or nonprimary)
- viral shedding and sexual transmission can occur during asymptomatic periods
- HIV-positive patients:
 - more frequent, prolonged, and/or severe episodes common with progressive immunosuppression; lesions may be atypical in appearance or location
 - viral shedding increases with declining CD4 counts (Augenbraun, 1995); may be more common in oral contraceptive or Depo-Provera users and in women with severe vitamin A deficiency (Mostad, 2000); most viral shedding asymptomatic
 - HSV is associated with increased risk for HIV transmission/acquisition (Heng, 1994)
- **Treatment:** See Table 6-5.
 - HIV-positive women often need higher doses (e.g., acyclovir 400 mg po 5 times/day or acyclovir 800 mg po 3 times/day) and longer treatment courses, particularly with more advanced immunosuppression, and may benefit from suppressive therapy.
 - Daily suppressive therapy reduces the frequency of recurrences by ≥ 75% among patients who suffer from frequent HSV episodes (i.e., six or more recurrences per year). Suppressive treatment reduces but does not eliminate viral shedding. Safety and efficacy with daily acyclovir for over 8 years.
 - Acyclovir-resistant HSV: Usually cross-resistant to famciclovir, valacyclovir. The CDC has reported a 6.4% resistance rate (Reyes, 1998). Most of these isolates are susceptible to foscarnet or

TABLE 6-5: RECOMMENDED MANAGEMENT FOR HSV

	<i>DRUG</i>	<i>DOSE</i>
First clinical episode	Acyclovir Acyclovir Famciclovir Valacyclovir	400 mg po three times a day for 7–10 days 200 mg po five times a day for 7–10 days 250 mg po three times a day for 7–10 days 1 g po twice a day for 7–10 days
Recurrent episodes	Acyclovir Acyclovir Acyclovir Famciclovir Valacyclovir	400 mg po three times a day for 5 days 200 mg po five times a day for 5 days 800 mg po twice a day for 5 days 125 mg po twice a day for 5 days 500 mg po twice a day for 5 days
Daily suppressive therapy	Acyclovir Famciclovir Valacyclovir Valacyclovir	400 mg po twice a day 250 mg po twice a day 500 mg po once a day 1000 mg po once a day
Severe disease	Acyclovir	5–10 mg/kg body weight IV every 8 hr for 5–7 days or until clinical resolution is achieved
Acyclovir-resistant HSV	Foscarnet Topical Cidofovir gel 1%	40 mg/kg body weight IV every 8 hr or 60 mg/kg IV every 12 hr for 3 wk applied to lesions once a day for 5 consecutive days

Source: CDC, 1998.

cidofovir. Factors associated with acyclovir resistance are low CD4 counts and long-term exposure to acyclovir.

Syphilis

- systemic disease caused by *Treponema pallidum*
- definitive methods for diagnosing early syphilis are darkfield examination and direct fluorescent antibody test of lesion exudate or tissue
- presumptive diagnosis is possible using two types of serologic tests for syphilis: VDRL or RPR (nontreponemal) and a confirmatory FTA-ABS or MHA-TP (treponemal)
- nontreponemal test antibody titers usually correlate with disease activity and are used to assess treatment response
- HIV-infected patients may have abnormal serologic test results (e.g., unusually high titers, false negatives or delayed seroreactivity). However, generally serologic tests can be interpreted in the usual manner. If clinical findings suggest syphilis but serology is nonreactive, biopsy, darkfield examination, or direct fluorescent antibody staining of lesion material should be considered. The clinical presentation of syphilis is very variable at all stages; atypical manifestations may be seen in the setting of HIV disease. Neurosyphilis should be considered in the differential diagnosis of neurologic signs or symptoms in HIV-infected individuals (CDC, 1998).
- **Treatment:** See Table 6-6.

TABLE 6-6: RECOMMENDED MANAGEMENT FOR SYPHILIS	
<i>STAGE</i>	<i>TREATMENT</i>
Primary and secondary syphilis and early latent syphilis	Benzathine penicillin G 2.4 million units IM (single dose); additional treatment recommended by some (i.e., three weekly doses of penicillin)
If penicillin-allergic (nonpregnant patients only)	Doxycycline 100 mg po twice a day for 2 wk, OR tetracycline 500 mg po 4 times a day for 2 wk
Late latent syphilis or syphilis of unknown duration (including tertiary syphilis)	Examination of the CSF must be performed before initiating treatment. If the CSF examination is negative, patients should be treated with 7.2 million units of benzathine penicillin G (three weekly doses of 2.4 million units each) IM
Neurosyphilis	Aqueous crystalline penicillin G 18–24 million units a day (administered as 3–4 million units IV every 4 hr) for 10–14 days. Administration of benzathine penicillin 2.4 million units IM after completion of the IV regimen recommended by some.
RECOMMENDED FOLLOW-UP	
<i>STAGE</i>	<i>FOLLOW-UP</i>
Primary and secondary syphilis	HIV-infected patients require clinical and serologic evaluation for treatment failure at 3, 6, 9, 12, and 24 mo after treatment. Treatment failures necessitate a CSF examination and retreatment (three weekly doses of 2.4 million units of benzathine penicillin G if CSF examination is negative). The latter regimen should also be considered for patients whose titers do not decrease fourfold within 6–12 mo.
Latent syphilis	HIV-infected patients require clinical and serologic evaluation at 6, 12, 18, and 24 mo after treatment. The CSF examination should be repeated and appropriate treatment instituted if clinical symptoms develop, titers rise fourfold, or if titers fail to decline fourfold between the evaluations at 12 and 24 mo.
Neurosyphilis	CSF examination should be repeated every 6 mo until the cell count is normal. Retreatment should be considered if the cell count has not decreased after 6 mo or if the CSF is not entirely normal after 2 yr.
CSF, cerebrospinal fluid. Source: CDC, 1998.	

Chancroid

- caused by *H. ducreyi*
- endemic in some areas of the United States; also occurs in discrete outbreaks
- 10% of patients with chancroid have coinfection with *T. pallidum* or HSV
- initial presentation typically consists of a tender papule that becomes pustular and then ulcerative; the ulcer is usually well demarcated, with ragged undermined edges
- probable diagnosis can be made if the patient has one or more painful ulcers, there is no evidence of *T. pallidum* or HSV infection, and the clinical presentation appearance of ulcers and regional lymphadenopathy is typical for chancroid
- Response to treatment may be diminished in the HIV-infected patient; may require longer courses of therapy, increased risk for treatment failure
- **Treatment:**
 - Azithromycin 1 g po (single dose), OR
 - Ceftriaxone 250 mg IM (single dose), OR
 - Ciprofloxacin 500 mg po twice a day for 3 days, OR
 - Erythromycin base 500 mg po four times a day for 7 days.
 - *Note*
 - ▶ In HIV-positive patients use single-dose therapies only if follow-up can be ensured;
 - ▶ Some experts recommend the 7-day erythromycin regimen in the setting of HIV infection.

Cytomegalovirus

- should be suspected in severely immunocompromised patients
- diagnosis requires biopsy of lesion with immunohistochemical stains
- cervical shedding of cytomegalovirus is associated with low CD4 counts (Clark, 1997)
- **Treatment:**
 - Ganciclovir 5 mg/kg IV twice a day for 2–3 wk, OR
 - Foscarnet 60 mg/kg IV q 8 hr or 90 mg/kg q 12 hr for 2–3 wk.

Other Infectious Causes of Genital Ulcers

- **Lymphogranuloma venereum:** rare in United States; associated with tender, usually unilateral inguinal or femoral lymphadenopathy, proctocolitis, rectal fistulas/strictures; diagnosis with serology and exclusion of

other causes; treatment: doxycycline or erythromycin for 3 wk; HIV-positive individuals may require more prolonged treatment

- **Granuloma inguinale (donovanosis):** rare in United States; painless, progressive ulcers which bleed easily on contact, without regional lymphadenopathy; diagnosis with biopsy or tissue crush preparation; treatment trimethoprim-sulfamethoxazole or doxycycline for 3 wk or until all lesions healed; CDC recommends adding aminoglycoside to regimen in HIV-positive patients
- **Tuberculosis** (Giannacopoulos, 1998): genital TB is generally a secondary manifestation of primary (usually pulmonary) disease. In the United States, the incidence of genital disease is < 1%. diagnosis is established by biopsy. Genital tuberculosis should be treated as is extrapulmonary disease; expert consultation is necessary.

INFLAMMATORY CONDITIONS

Crohn's Disease

- This disease may be easily misdiagnosed because its principal clinical features (i.e., fever, abdominal pain, diarrhea, fatigability, weight loss) are often found in patients with HIV disease. 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 and 10 mm in diameter, and they can be shallow or deep with a central yellowish necrotic base; either a single lesion or crops of lesions may be evident. Diagnosis is established based on the clinical presentation and biopsy. Treatment consists of topical or systemic corticosteroids.

Hidradenitis suppurativa (Droegemueller, 1997)

- 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 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, topical steroids, anti-androgens, and isotretinoin. Treatment of advanced disease requires surgical intervention.

NEOPLASTIC

- any nonhealing genital ulcer must be biopsied to rule out a neoplastic process
- squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, melanoma, lymphoma, Kaposi's sarcoma
- refer to oncologist

DRUG REACTION

- has been described as rare side effect of treatment with zalcitibine and foscarnet

APHTHOUS GENITAL ULCERATIONS (Anderson, 1996a)

- no specific etiology (typical or opportunistic organism) is identifiable
- similar to aphthous ulcers seen in the gastrointestinal tract
- most patients are significantly immunosuppressed (median CD4 count 50/mm³)
- lesions can be painful, multiple, deep, and extensive (size 1–6 cm)
- associated morbidity includes immobility, bleeding, and superinfection
- most have been reported to be chronic and/or recurrent or relapsing
- oroesophageal ulcers coexist in about one third of cases and one fifth were associated with genital fistula formation

■ Treatment:

- Consider empiric therapy for HSV.
- If empiric therapy fails, systemic steroids (prednisone 40–60 mg/day for 1–2 wk, then taper) have been moderately successful.
- Thalidomide (200 mg/day for 2–4 wk) has been used in similar ulcers in the oropharynx or esophagus with complete healing in 55–73% of these ulcers (Jacobson, 1997, 1999); there has been similar success anecdotally in genital aphthous ulcers. (Warning: this drug is a powerful teratogen and should only be used in women of reproductive age after appropriate counseling and pregnancy testing and in the setting of reliable contraception or abstinence.)

TRAUMA

- history of traumatic injury
- consider possibility of sexual violence

V. VAGINAL DISCHARGE

A. HISTORY

Duration and characteristics of discharge, associated symptoms (e.g., pruritus, malodor, burning, pelvic pain), sexual history (including condom and other contraceptive use), history of sexually transmitted diseases, history of douching, recent antibiotic use, CD4 counts and HIV-RNA levels, medications.

B. PHYSICAL EXAM

Complete genital inspection and bimanual pelvic examination; document the characteristics and amount of discharge as well as the presence of erythema, edema, and tenderness.

C. EVALUATION

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

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

BACTERIAL VAGINOSIS (BV)

- most prevalent cause of vaginal discharge or malodor
- results from replacement of normal *Lactobacillus* dominant vaginal flora with increase in prevalence and concentration of mixed flora, including anaerobic bacteria, *Gardnerella vaginalis*, and *Mycoplasma hominis*
- 18–42% prevalence among HIV-infected women; no significant difference compared with HIV-negative controls and no difference by CD4 count (Cu-Uvin, 1999; Greenblatt, 1999)
- some studies suggest that BV or BV-associated organisms (or lack of vaginal lactobacilli) may enhance HIV transmission (Martin, 1999; Olinger, 1999)
- associated with increase in several obstetric and gynecologic complications, including pelvic inflammatory disease (PID), postabortion and posthysterectomy infections, preterm labor
- standard diagnosis by clinical criteria; requires three of the following:
 - 1) a homogeneous grayish or yellowish discharge (may coat vaginal walls);

2) clue cells on microscopic examination; 3) vaginal pH > 4.5; 4) a positive whiff test (i.e., fishy odor of discharge before or after addition of 10% KOH)

■ **Treatment:** See Table 6-7.

TABLE 6-7: RECOMMENDED MANAGEMENT FOR BACTERIAL VAGINOSIS
■ Metronidazole 500 mg po twice a day for 7 days
■ Clindamycin cream 2%, 5 g intravaginally at bedtime for 7 days
■ Metronidazole gel 0.75%, 5 g intravaginally twice a day for 5 days
<i>Note:</i> Clindamycin cream is oil-based and may weaken latex condoms and diaphragms. Alternative regimens: metronidazole 2 g po or clindamycin 300 mg po twice a day for 7 days.
<i>Source:</i> CDC, 1998.

VULVOVAGINAL CANDIDIASIS

- Most commonly caused by *Candida albicans*, the prevalence of infections due to nonalbicans species is increasing
- 75% of all women will have at least one episode of candidiasis, and 40–45% will have two or more episodes; less than 5% of women experience recurrent episodes of candidiasis
- typical symptoms: thick, white discharge and pruritus; other symptoms include vulvar burning, vaginal soreness, dyspareunia, and external dysuria
- Prevalence among HIV-infected women is 3–15%; most studies suggest no significant difference in prevalence of infection between relatively immunocompetent HIV-positive women and HIV-negative controls; several other studies have found increasing infection rates with declining CD4 counts (Cu-Uvin, 1999; Duerr, 1997). HIV-positive women may have higher incidence of infection (El-Sadr, 1997).
- Possible confounding factor for HIV-positive women is more frequent use of antibiotics
- Most studies show increased rates of vaginal (also rectal, oral) colonization in HIV-positive women, particularly with declining immune function; no data on relationship between HIV-RNA levels and candidiasis or colonization
- In HIV-positive women 26–27% of vaginal isolates are non-*albicans* strains (Schuman, 1998); available studies are conflicting on the proportion of non-*albicans* strains in HIV-positive compared with HIV-negative women; most common is *Torulopsis glabrata*. No association found to date between strain diversity and HIV progression
- Diagnosis is made by identifying budding yeast or pseudohyphae on a wet mount or KOH preparation or Gram stain of vaginal discharge; positive identification can also be accomplished by means of culture

TABLE 6-8: RECOMMENDED MANAGEMENT FOR VULVOVAGINAL CANDIDIASIS

TOPICAL AZOLES
■ Butoconazole 2% cream 5 g PV for 3 days*
■ Clotrimazole 1% cream 5 g PV for 7–14 days*
■ Clotrimazole 100 mg vaginal tablet for 7 days
■ Clotrimazole 100 mg vaginal tablet, 2 tablets for 3 days
■ Clotrimazole 500 mg vaginal tablet x 1
■ Miconazole 2% cream 5 g PV for 7 days*
■ Miconazole 200 mg vaginal suppository for 3 days*
■ Miconazole 100 mg vaginal suppository for 7 days*
■ Miconazole 1200 mg vaginal suppository x 1
■ Tioconazole 6.5% ointment 5 g PV x 1*
■ Tioconazole 2% cream 5 g PV for 3 days
■ Terconazole 0.4% cream 5 g PV for 7 days
■ Terconazole 0.8% cream PV for 3 days
■ Terconazole 80 mg vaginal suppository for 3 days
* Available over the counter. PV, vaginally. <i>Note:</i> These creams are oil-based and may weaken latex condoms and diaphragms.
ORAL AGENT[†]
■ Fluconazole 150 mg po x 1
[†] Avoid concomitant use with terfenadine, astemizole, cisapride secondary to cardiotoxicity.
OTHERS
■ Nystatin 100,000 unit vaginal tablet, one tablet for 14 days (less effective)
■ 1% Gentian violet applied to vagina 4 times at intervals of approximately 7 days [‡]
■ Boric acid 600 mg intravaginal capsules bid for 2 wk [‡]
[‡] May be useful in chronic/recurrent cases; gentian violet messy, causes mucosal exfoliation; encourage abstinence during treatment; reinforce condom use.

■ **Treatment:** See Table 6-8.

● **Special considerations in HIV-positive women:**

- ▶ Topical therapies may be more effective when given for at least 7 days
- ▶ Consider prophylactic use of topical antifungals when antibiotics are given
- ▶ Randomized, placebo-controlled trial of fluconazole 200 mg po weekly for prophylaxis of candidiasis in women with CD4 < 300/mm³ (median CD4 15/mm³): effective in preventing oropharyngeal candidiasis (relative risk .50, p < .001) and vaginal candidiasis (relative risk .64, p = .05), but not esophageal candidiasis (Schuman, 1997a). Consider in selected cases with recurrent vaginal candidiasis.

► Recent study found that ritonavir and indinavir (and possibly other protease inhibitors) strongly inhibited secretory aspartyl proteinase (proteolytic enzyme produced by pathogenic *Candida* species, considered a virulence factor) activity and production in a dose-dependent fashion, and exerted a therapeutic effect in an experimental model of vaginal candidiasis, with efficacy similar to fluconazole (Cassone, 1999).

● **Azole resistance:**

Concerns have been raised about extensive use of oral azoles and promotion of azole resistance, possibly limiting use of these agents for other HIV-related indications. Current information about development of resistance is limited.

- ACTG 816: annual incidence of clinical failure to fluconazole (persistence of oral candidiasis after 200 mg/day or higher dose for 14 days) 5.8% (median CD4 15/mm³); *C. albicans* primary etiology
- Community Programs for Clinical Research on AIDS-randomized, placebo-controlled trial of fluconazole 200 mg weekly for prophylaxis of candidiasis (described above) (median CD4 15/mm³): after median 29 mo follow-up, fluconazole resistance < 5% resistance in both fluconazole and placebo groups (Schuman, 1997a)
- HIV Epidemiology Research Study (HERS): overall fluconazole resistance rare among *C. albicans* isolates, but frequent in non-*albicans* isolates from vagina and oral cavity; fluconazole resistance with non-*albicans* species more likely in HIV-positive women; not significantly related to CD4 count. Resistance among non-*albicans* species stable after 1 yr of follow-up (Schuman, 1997b)
- 139 isolates from vulvovaginal candidiasis in HIV-positive women: 95–98% susceptibility of *C. albicans* to fluconazole, itraconazole, clotrimazole; *T. glabrata*: 44% resistance to fluconazole, 72% resistance to itraconazole and clotrimazole. Twenty percent of 90 relapses/persistence were with same organism; emergence of drug resistance was not observed between sequential isolates. Twelve percent had recurrent infection with different strains or species (Li, 1997).

There are no current data to suggest that intermittent therapy with a single dose of fluconazole increases development of azole resistance. Similarly, weekly prophylaxis with fluconazole was associated with infrequent development of resistance, which was not significantly different from placebo recipients. Nevertheless, long-term use of fluconazole may select for more resistant and difficult-to-treat non-*albicans* species and should be used with caution. Further study is needed.

- **Recurrent candidiasis** (four or more symptomatic episodes per year):

- ▶ Evaluation:

1. establish diagnosis — fungal culture may be needed
2. identify/eliminate predisposing factors, if possible: uncontrolled diabetes, corticosteroid use, topical or systemic antibiotics, spermicides (conflicting data), tight-fitting synthetic underwear, douching, pregnancy, immunosuppression
3. speciation/susceptibility testing

- ▶ Management options:

1. longer duration of standard treatment regimen
2. chronic intermittent therapy (e.g., with perimenstrual episodes)
3. restriction of orogenital/anogenital sexual contact (anecdotal evidence only); double-blind, placebo-controlled trials of topical therapy for male sexual partners showed no benefit (Sobel, 1999)
4. possible role for boric acid vaginal capsules, gentian violet
5. maintenance therapy: initial intensive regimen for 10–14 days followed by a maintenance regimen for at least 6 mo:
 - a. fluconazole* 100–200 mg po every wk
 - b. itraconazole* 50–100 mg po every wk
 - c. clotrimazole 500 mg suppository per vagina every wk
 - d. ketoconazole* 100 mg po every day (associated with rare but significant hepatotoxicity—monitor liver function; significant drug interactions with some antiretrovirals (see Chapter XIV on Pharmacologic Considerations in HIV-infected Pregnant Patients))
6. immune reconstitution; potential benefit with protease inhibitors

* *Note* avoid concomitant use with terfenadine, astemizole, cisapride secondary to cardiotoxicity.

TRICHOMONIASIS

- Caused by *Trichomonas vaginalis*

- HIV-positive women: 5–23% prevalence; studies have not shown increased prevalence compared with HIV-negative women; incidence in HIV-positive women 10–17% (Minkoff, 1999; Sorvillo, 1998)

- Clinical features: profuse, malodorous, often frothy, yellow-green discharge and vulvar irritation; may have urinary symptoms or dyspareunia; signs of inflammation — vaginal erythema, “strawberry” vagina, cervix with punctate hemorrhages; may be asymptomatic in chronic cases

- **Diagnosis:** saline wet mount (motile trichomonads seen in 50–70% culture-positive cases); Pap smear (60–70% sensitivity, false positives not uncommon); culture (95% sensitivity); DNA probes; monoclonal antibodies
- ***T. vaginalis*** cysteine proteases degrade and render nonfunctional secretory leukocyte protease inhibitor, a substance thought to protect mucosal surfaces from HIV transmission by inhibition of HIV protease activity necessary for infection of monocytes and macrophages (Draper, 1998)
- **Treatment (CDC,1998):**
 - Metronidazole 2 g po (single dose), OR
 - Metronidazole 500 mg po twice a day for 7 days
 - **Note:**
 - ▶ No change in treatment based on HIV status
 - ▶ Sex partners should be treated with the same regimen (> 90% cure rates can be expected if partner is treated simultaneously); intercourse should be avoided until therapy is complete and patient and partner are asymptomatic
 - ▶ Topical metronidazole less effective
 - ▶ Metronidazole resistance is rare; organisms with decreased susceptibility usually respond to higher doses of metronidazole. If treatment failure occurs with either regimen, retreat with metronidazole 500 mg po twice a day for 7 days. If treatment failure occurs repeatedly, treat with metronidazole 2 g po once a day for 3–5 days. Patients with documented infection (with reinfection excluded) who have not responded to these measures should be managed in consultation with an expert.

GONORRHEA

- caused by *Neisseria gonorrhoeae*
- **clinical presentation:** commonly asymptomatic; vaginal discharge may be present; if untreated, 10–20% develop PID; urethra is primary site of colonization after hysterectomy and should be sampled with culture or DNA probe for testing in these patients; gonorrhea may also cause rectal infection, pharyngitis, and (rarely) disseminated infection
- **diagnosis:** culture, DNA probe, polymerase chain reaction (PCR) or ligase chain reaction (LCR). PCR/LCR can be used with cervical, urethral, or urine specimens; may detect gonorrhea and chlamydia simultaneously; sensitivity 93–98%, specificity > 99%; able to detect 15–40% more infections than culture (Hook, 1999)
- **prevalence/clinical presentation/diagnosis/treatment in HIV-positive patients:** no difference compared with HIV-negative patients

■ Treatment (CDC,1998):

- Cefixime 400 mg po (single dose), OR
- Ceftriaxone 125 mg IM (single dose), OR
- Ciprofloxacin 500 mg po (single dose), OR
- Ofloxacin 400 mg po (single dose).
- **Alternative regimen:**
 - ▶ Spectinomycin 2 g IM (single dose)
- **Note:**
 - ▶ It is recommended that women be presumptively treated for chlamydia, particularly in areas with high rates of coinfection, absence of chlamydial testing, and/or when patient may not return for results
 - ▶ Sex partners should be treated for both gonorrhea and chlamydia if their last sexual contact 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 recommended after apparent treatment failure with standard regimen
 - ▶ Avoid use of quinolones and tetracyclines in pregnancy

CHLAMYDIA**■ caused by *Chlamydia trachomatis***

- clinical presentation: asymptomatic infection common; abnormal discharge; symptoms of urethritis; if untreated, 10–40% develop PID
- diagnosis: culture (cell based), antigen detection, DNA probe, PCR/LCR (90–100% sensitivity — see above) (Stamm, 1999)
- prevalence/clinical presentation/diagnosis/treatment in HIV-positive women: no differences compared with HIV-negative women
- **Treatment (CDC,1998):**

- Azithromycin 1 g po (single dose), OR
- Doxycycline 100 mg po twice a day for 7 days
- Alternative regimens:
 - ▶ Erythromycin base 500 mg po four times a day for 7 days OR
 - ▶ Erythromycin ethylsuccinate 800 mg po four times a day for 7 days, OR
 - ▶ Ofloxacin 300 mg po twice a day for 7 days.

- *Note:*

- ▶ Recommendations for the management of sex partners are the same as for gonorrhea (see above)
- ▶ Avoid use of doxycycline or quinolones in pregnancy

OTHER

- Atrophic vaginitis: related to estrogen deficiency; 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 (retained tampon, toilet paper, etc.)
- Local irritants (spermicides, vaginal medications, toilet paper dye, hygiene sprays, soap, detergent, douches, etc.)

VI. PELVIC/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 mo duration. **Cyclic pain** is associated with the menstrual cycle.

A. HISTORY

Characteristics of pain: onset (rapid or gradual), character (crampy, colicky, sharp or dull), location (generalized or localized pain) and duration; associated symptoms: abnormal vaginal bleeding or discharge, gastrointestinal symptoms (e.g., nausea/vomiting, anorexia, constipation, diarrhea), and urinary (e.g., dysuria, frequency, urgency, hematuria) symptoms, fever or chills; history of other medical conditions; surgical history; gynecologic history: date of last menstrual period, use of contraception and condoms, history of STDs; medications; CD4 counts and HIV-RNA levels.

B. PHYSICAL EXAM

A complete set of vital signs should be obtained. The physical exam should focus on abdominal and pelvic findings. A complete abdominal exam should evaluate the presence and character of bowel sounds, distention, suprapubic or costovertebral angle tenderness, other abdominal tenderness (including rebound and guarding), and presence of masses. The pelvic exam should determine the 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 should be ruled out.

C. EVALUATION

- Pregnancy test
- Laboratory tests: CBC with differential, sedimentation rate, chemistry panel, others as indicated
- Wet mount/STD testing
- Urinalysis and urine culture
- Stool studies (cultures, evaluation for ova and parasites, *C. difficile* toxin assay) — if indicated by GI symptomatology
- Pelvic ultrasound, computed tomography (CT) scans — if indicated
- Blood cultures — bacteria, *Mycobacterium avium*, if indicated

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

Includes but is not limited to:

- **Pregnancy:** refer
- **Pelvic inflammatory disease:** PID is an upper genital tract infection, usually polymicrobial in nature. Sexually transmitted organisms, including *N. gonorrhoea* and *C. trachomatis*, are implicated in most cases of PID; bacterial vaginosis-associated organisms are also commonly present. 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). Current CDC-recommended criteria for diagnosis of PID are (CDC,1998):

- **Minimum criteria:**

- ▶ lower abdominal tenderness
- ▶ adnexal tenderness
- ▶ cervical motion tenderness

Because of difficulty in diagnosis and the potential for long-term complications, empiric therapy should be initiated if these criteria are present and no other cause for symptoms is identified.

- **Additional criteria:**

- ▶ oral temperature > 101°F (> 38.3°C)
- ▶ abnormal cervical or vaginal discharge
- ▶ elevated erythrocyte sedimentation rate
- ▶ elevated C-reactive protein
- ▶ documented cervical gonorrhea or chlamydia infection

These criteria enhance specificity.

- **Definitive criteria:**

- ▶ endometritis on endometrial biopsy
- ▶ tuboovarian complex or thickened, fluid-filled tubes on transvaginal ultrasound
- ▶ laparoscopic abnormalities consistent with PID

Warranted in patients who are severely ill and/or when diagnosis is uncertain.

- **PID in the HIV-positive woman:** Several studies have found increased seroprevalence of HIV in hospitalized PID patients (Hoegsberg, 1990; Sperling, 1991). A recent analysis of hysterectomy specimens from HIV-positive women and HIV-negative women, matched for surgical indication, found chronic endometritis twice as commonly in the HIV-positive specimens; some degree of abnormal uterine bleeding had occurred in all cases (Kerr-Layton, 1998). Moreover, the clinical presentation among these women may be more severe or otherwise altered (e.g., lower white blood cell counts than HIV-negative women) (Barbosa, 1997; Cohen, 1998; Kamenga, 1995); in African studies, more severe illness, including tuboovarian abscess, and longer hospital stays were found with significant immunosuppression. The microbiology of infection and response to standard antibiotic regimens are similar to HIV-uninfected women; however, some studies have reported a greater need for surgical intervention (Korn, 1993). CMV and tuberculosis may cause upper genital tract infection in rare cases and should be considered in appropriate clinical situations. Current CDC recommendations call for managing immunosuppressed HIV-infected women with PID aggressively with a parenteral regimen. A more recent study from Kenya found similar efficacy of oral ambulatory therapy in HIV-positive and HIV-negative women with PID (Bukusi, 1999). Decisions about oral vs. parenteral therapy should be individualized.

- **Treatment (CDC,1998):**

- ▶ **Parenteral regimens:**

- ◆ Cefotetan 2 g IV every 12 hr, PLUS doxycycline 100 mg IV, OR
- ◆ Cefoxitin 2 g IV every 6 hr, PLUS doxycycline 100 mg IV, OR
- ◆ Clindamycin 900 mg IV every 8 hr, PLUS gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hr

TABLE 6-9: INDICATIONS FOR HOSPITALIZATION IN PATIENTS WITH PID

■ Inadequate response to outpatient therapy
■ Uncertain diagnosis; surgical emergency cannot be excluded
■ Pregnancy
■ Inability to tolerate or follow outpatient regimen
■ Immunosuppression (low CD4 counts, clinical AIDS, on immunosuppressive drugs, other significant comorbidity)
■ Tuboovarian abscess or other evidence of severe illness, nausea and vomiting, or high fever

► **Oral regimens:**

- ◆ Ofloxacin 400 mg orally twice a day for 14 days, PLUS metronidazole 500 mg orally twice a day for 14 days, OR
- ◆ Ceftriaxone 250 mg IM, OR
- ◆ Cefoxitin 2 g IM once plus probenecid 1 g orally in a single dose concurrently once, PLUS doxycycline 100 mg orally twice a day for 14 days

For alternative oral and parenteral regimens, please see the CDC 1998 Guidelines for Treatment of Sexually Transmitted Diseases.

Parenteral therapy may be discontinued 24 hr after there is evidence of clinical improvement. Oral therapy with doxycycline 100 mg every 12 hr (consider the addition of Metronidazole 500 mg every 12 hr, particularly with presence of tuboovarian abscess) or clindamycin 450 mg four times a day should then be instituted to complete a 14-day treatment course. Sexual partners of women diagnosed with PID should be evaluated and treated presumptively for gonorrhea and chlamydia if they have had sexual contact within the 60 days preceding the onset of symptoms.

- **Ruptured/hemorrhagic ovarian cyst:** can cause acute abdominal pain; bleeding associated with rupture is usually self-limited but may require surgical intervention.
- **Ovarian torsion:** acute, severe, unilateral lower abdominal/pelvic pain, often with history of previous similar episodes; palpable adnexal mass often present. Surgical intervention required.
- **Uterine uterine leiomyomas (fibroids)leiomyomas (fibroids):** may cause pain with rapid enlargement, degeneration, or torsion; referral indicated
- **Endometriosis:** cause of acute or chronic pain, usually includes secondary dysmenorrhea and/or dyspareunia; referral to gynecologic specialist indicated if endometriosis suspected
- **Dysmenorrhea:** affects about half of all menstruating women; cyclic pain with menses. 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 antiinflammatory drugs (NSAIDs)

(80% effective) or oral contraceptive pills (90% effective). Treatment of secondary dysmenorrhea is directed at the specific underlying problem.

- **Mittelschmerz:** pain with ovulation, generally self-limited; manage with NSAIDs
- **Gastrointestinal pathology:** includes appendicitis; diverticulitis (pain generally localizes to the left lower quadrant; usually seen at older ages); irritable bowel syndrome (pain is usually intermittent, cramp-like, and more common in the left lower quadrant; exacerbated by certain foods); inflammatory bowel disease; infectious enterocolitis (pain, cramping, diarrhea); obstruction (colicky pain, distention, vomiting, obstipation). Opportunistic infections, including cryptosporidia, CMV, and *M. avium* may be causes of chronic diarrhea in patients with AIDS, and clinical features usually include abdominal pain.
- **Urinary tract pathology:** renal/ureteral stones, cystitis, and pyelonephritis
- **Medication-related:** indinavir (renal stones); didanosine (pancreatitis)

VII. PELVIC MASS

A. 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), or constitutional symptoms (e.g., fever, chills, weight loss or gain).

B. PHYSICAL EXAM

A complete abdominal and pelvic examination should be performed, with particular attention given to the size, location, mobility, and characteristics of the mass (if palpable) as well as to signs of ascites; lymph node survey. With functional ovarian cysts, a normal ovary may be up to 5–6 cm in size for a woman in the reproductive age range. A palpable ovary in a postmenopausal woman is abnormal and requires further evaluation.

C. EVALUATION

- Pregnancy test: if premenopausal
- Laboratory tests: CBC with differential; chemistry panel; tumor markers, if indicated (e.g., CEA, Ca-125; frequent false positives and false negatives, should only be used in conjunction with other diagnostic procedures)
- Radiologic studies: pelvic ultrasound (transabdominal/transvaginal), CT, and magnetic resonance imaging (MRI), as indicated. Ultrasound is generally the first diagnostic modality employed in evaluating pelvic anatomy; concerning characteristics include complex or solid mass, presence of ascites. CT/MRI are better at imaging GI tract, retroperitoneal lymphadenopathy, liver

Additional evaluation involving procedures such as laparoscopy, colonoscopy, etc., require referral to appropriate specialists.

D. DIFFERENTIAL DIAGNOSIS

- **Ectopic pregnancy:** the primary consideration in the setting of an adnexal mass and a positive pregnancy test.
- **Ovarian functional cyst:** Functional cysts are the most common ovarian masses found among women of reproductive age; resolution occurs spontaneously in 1–3 mo.
- **Uterine leiomyomas (fibroids):** often asymptomatic, but may be associated with heavy and/or prolonged menses, urinary frequency.
- **Endometrioma:** consider in women with a documented or suspected history of endometriosis.
- **Hydrosalpinx/pyosalpinx and tuboovarian abscess:** consider with history suggestive of PID; initial management with broad-spectrum antibiotics.
- **Benign or malignant ovarian neoplasm:** Surgical intervention is required. No evidence of increased prevalence in HIV-positive women; anecdotal reports suggest ovarian cancer may present at more advanced stage, with poorer response to cytoreductive surgery and chemotherapy (Rojansky, 1996). Non-Hodgkins lymphoma of ovary described in an HIV-positive woman (Neary, 1996).
- **Retroperitoneal lymphadenopathy:** may present as pelvic mass; possible causes include tuberculosis, lymphoma
- **Gastrointestinal masses:** includes diverticular abscess, bowel malignancy

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

VIII. URINARY SYMPTOMS

A. HISTORY

Duration and severity of urinary symptoms; specific symptoms: dysuria, frequency, urgency, hematuria, nocturia, incontinence; associated symptoms, including pain (suprapubic or flank), fever, chills, and weight loss; other medical conditions (e.g., diabetes, sickle cell disease); surgical history; medications; CD4 count and HIV-RNA level

B. PHYSICAL EXAM

Vital signs; document presence of suprapubic tenderness or flank or costovertebral angle tenderness

C. EVALUATION

- Microscopic exam of urine
- Urine culture and sensitivity
- Gonorrhea/chlamydia testing, if indicated
- Urine cytology: consider in woman over age 50 who presents with irritative symptoms or hematuria and negative culture
- Urine for acid-fast bacillus (AFB) culture, purified protein derivative (PPD): if indicated, urinary TB suspected
- Intravenous pyelogram (IVP): if indicated; consider if stones, urinary tract anomalies, or urinary TB suspected
- Other tests: cystoscopy, urodynamics — refer to appropriate specialist

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

- **Bacterial urinary tract infection:** lower tract (cystitis) or upper tract (pyelonephritis); may be asymptomatic and clinical signs and symptoms cannot reliably distinguish between upper and lower tract infection. Classically cystitis characterized by the presence of dull, suprapubic pain; typical associated symptoms include dysuria, urinary frequency and urgency, and occasionally hematuria. Pyelonephritis associated with flank or costovertebral pain and tenderness to percussion, as well as systemic signs/symptoms, including fever, chills, nausea, vomiting, 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/ureteral stones:** severe, colicky pain; usually associated with urinary stasis or chronic infection, although may be related to metabolic abnormalities, such as gout or problems with calcium homeostasis; a significant side effect associated with indinavir therapy.
- **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 for definitive evaluation
- **Urinary tuberculosis:** one of the most common sites of extrapulmonary TB; gross or microscopic hematuria and pyuria with negative bacterial culture should lead to consideration; manage with expert consultation
- **Tumors:** most common presenting complaint is gross or microscopic hematuria; hematuria without identifiable etiology (e.g., infection) requires referral to 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. Rule out infection with culture and “overflow” incontinence (secondary to overdistended bladder) with postvoid catheterization for residual urine determination. Further evaluation requires referral to urogynecologist or urologist
- **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)

IX. 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 section on abnormal Pap smear, above).

A. HISTORY

Location of warts, duration, and the presence of associated symptoms (itching, irritation, pain, bleeding); history of prior occurrences of similar lesions and their treatment; history of abnormal Pap smear results

B. PHYSICAL EXAM

Complete examination of the external genitalia as well as of the cervix, vagina, and perianal region should be performed; location and size of warts should be documented. 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.

C. RELATION TO HIV

HIV-infected women are more likely to have HPV coinfection and both prevalence and incidence of genital warts are increased compared with HIV-negative women (Chirgwin, 1995). Both prevalence and clinical expression of HPV increase with progressive clinical disease and immunologic decline. Immunosuppressed women may not respond as well to treatment and have more frequent recurrences after therapy. Squamous cell carcinomas that arise in or resemble genital warts may occur more commonly in the setting of immunosuppression, making confirmation of diagnosis with biopsy more frequently necessary.

D. EVALUATION

- **Biopsy:** Typical condyloma accuminata are diagnosed by inspection and do not require biopsy. A biopsy of the lesion and histopathologic confirmation of the diagnosis are 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
- **Colposcopy:** Colposcopy and directed biopsies of the entire lower genital tract should be considered in HIV-positive women with evidence of HPV infection. Colposcopy should be performed to rule out the presence of high-grade squamous intraepithelial lesions 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, have an effect on 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 treatment modality depends on the number, size, and location of the warts. When there are a small number of lesions and they are fairly small, a topical agent may be employed. Table 6-10 displays provider-applied and patient-administered regimens recommended by the CDC (CDC, 1998).

<i>PROVIDER-APPLIED</i>	<i>PATIENT-APPLIED</i>
80–90% trichloroacetic acid (weekly if necessary) Cryotherapy with liquid nitrogen or cryoprobe—repeat every 1–2 wk	Podofilox .5% solution or gel applied twice a day for 3 days followed by 4 days of no therapy. May repeat application for up to 4 cycles; application should be limited to .5 mL per day and < 10 cm ² area of warts
10–25% podophyllin resin (weekly if necessary). Application should be limited to < .5 mL of podophyllin or < 10 cm ² of warts per session and preparation should be thoroughly washed off 1–4 hr after application to reduce local irritation. Because of concern about potential systemic absorption and toxicity, avoid use on mucosal surfaces.	Imiquimod 5% cream applied three times per wk for as long as 16 wk. The treated area should be washed with mild soap and water 6–10 hr after application.
Surgical removal (laser or excision)	
<i>Note:</i> Avoid use of podophyllin, podofilox, and imiquimod during pregnancy.	

Most treatment modalities are associated with mild to moderate discomfort and local irritation. Intralesional interferon is an additional alternative treatment but is expensive and associated with a high frequency of systemic side effects. Treatment method should be changed if there is not substantial improvement after three provider-administered treatments or if there is not complete clearance after six treatments. Combining modalities does not appear to 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, referral for possible laser surgery should be considered. In one study relapse rates of treated genital warts in HIV-positive patients was lower in those on combination antiretroviral therapy and was correlated with HIV-RNA levels (Giovanna, 1998).

X. GENITAL MASSES/NODULES

A. 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 presence of similar lesions on genitals of partner); medications; CD4 count and HIV-RNA level

B. PHYSICAL EXAM

Document anatomic location, number, and size of the nodules; presence of associated edema, erythema, induration, fluctuance, tenderness, discharge, or bleeding

C. EVALUATION

Biopsy indicated if etiology is unclear; culture of abscess contents

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

- **Bartholin's abscess:** Bartholin's glands are normally nonpalpable and located deep in the perineum at the 5 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 abscess; exquisitely tender. Treatment consists of incision and drainage.
- **Molluscum contagiosum:** an asymptomatic viral disease that primarily affects skin of the vulva, although it can present as a generalized skin disease in immunosuppressed individuals; spread by close contact, both sexual and nonsexual. Clinical features: small nodules or domed papules, usually 1–5 mm in diameter; the more mature nodules appear to have an umbilicated center. This disease tends to be self-limited; however, disease course

may be complicated by repeat infection and autoinoculation of the virus. Treatment consists of serial applications of liquid nitrogen or of removal of the nodules with a dermal curet and chemical cauterization of base with 85% trichloroacetic acid or ferric subsulfate. Molluscum contagiosum affects 5–10% of HIV-positive patients; extensive, severe lesions that show poor response to therapy are common; such unresponsive lesions, however, have been found to regress with HAART (Calista, 1999).

- **Tumors, other masses:** biopsy required; expert consultation indicated.

XI. GENITAL ITCHING/IRRITATION

A. HISTORY

Duration, location, and severity of pruritis/irritation; associated symptoms (erythema, edema, vulvar burning, dysuria, dyspareunia); prior episodes of similar symptoms and treatment; exposure to particular agents (e.g., soaps, sprays, vaginal contraceptives, douches, colored toilet tissue, etc.) coincident with the beginning of symptoms; presence of similar symptoms in close contacts; medications, including antibiotics; CD4 count and HIV-RNA level

B. PHYSICAL EXAM

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

C. EVALUATION

- Fungal culture/KOH preparation: indicated if a fungal infection is suspected.
- HSV culture: herpes may appear atypically and should be ruled out in the presence of vesicular lesions, unexplained abrasions, or fissuring, or if warranted by history.
- Skin scrapings: scraping of skin papule is 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.

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

- **Fungal infection:** Although the primary symptom associated with fungal infections is itching, women also complain of vulvar burning, dysuria, and dyspareunia, particularly with involvement of vulvar skin. Examination often reveals edema, erythema, and excoriation; pustular lesions may be

found to extend beyond the line of erythema when extensive skin involvement is present. Diagnosis is established by means of a KOH preparation or fungal culture. Treatment is topical application of an antifungal preparation. (See vulvovaginal candidiasis in the Vaginal Discharge section above.)

- **Allergic/irritative reaction:** Contact dermatitis frequently affects the vulvar skin, particularly the intertriginous areas; etiologic agents include urine or feces, latex, semen, 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. Examination of the skin reveals erythema, edema, and inflammation; the skin may be weeping and eczematoid. Secondary infection may occur.

Treatment involves removing the offending agent. Severe lesions may be treated with wet compresses of Burow's solution diluted 1:20 for 30 min several times a day. If possible, the vulva should be dried with cool air from a hair dryer following 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% to 1%) or fluorinated corticosteroid (Valisone 0.1% or Synalar 0.01%) lotions or creams into 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/lice:

- Scabies is a parasitic infection produced by the itch mite, *Sarcoptes scabiei*. The main symptom reported is severe, intermittent itching that tends to be more intense at night. Lesions can present as vesicles, papules, or burrows; any area of skin may be affected: the hands, wrists, breasts, vulva, and buttocks are most often affected. HIV-infected and other immunosuppressed patients are at increased risk for Norwegian scabies, a disseminated dermatologic infection; this can appear classically as hyperkeratotic, nonpruritic lesions; as crusting with pruritus; a pruritic, papular dermatitis; or lesions resembling psoriasis (Schlesinger, 1994).

▶ CDC-recommended treatment for scabies (CDC, 1998):

- ◆ Permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8–14 hr.

▶ Alternative regimens:

- ◆ 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 hr OR sulfur (6%) precipitated in ointment

applied thinly to all areas nightly for 3 nights; previous applications should be washed off before new applications are applied. Thoroughly wash off 24 hr after last application.

- ◆ Lindane should not be used by pregnant or lactating women or after a bath.

Itching may persist for days following treatment; antihistamine therapy should be considered for symptomatic relief. Norwegian scabies should be managed in consultation with an expert.

- Pediculosis pubis is due to infestation by 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 (eyelids are occasionally infested). The presenting symptom is constant itching in the pubic area. 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.

- ▶ The CDC-recommended treatment (CDC, 1998) is permethrin 1% cream rinse applied to affected areas and washed off after 10 min. Alternatively, lindane 1% shampoo (applied for 4 min and thoroughly washed off; lindane not recommended for pregnant or lactating women) OR pyrethrins with piperonyl butoxide (applied to the affected area and washed off after 10 min). If symptoms do not resolve, patients should be reexamined in 1 wk; if lice or eggs are seen at the hair-skin junction, the patient should be retreated. All clothing and bedding must be decontaminated. Close household contacts and sexual contacts (within the previous month) should be treated.

XII. BREAST LUMP

A. HISTORY

If palpable by the patient, duration of the lump; any associated symptoms (e.g., tenderness, nipple discharge, cyclic pain); changes in the characteristics of the lump (e.g., increase in size); history of previous breast lumps; family history of breast disease or cancer.

B. PHYSICAL EXAM

Symmetry, contour, and appearance of the skin; presence of edema, erythema, skin dimpling, or nipple retraction; presence and size of dominant masses, nodularity, tenderness; nipple discharge (including color); and lymphadenopathy (axillary and supraclavicular).

C. EVALUATION

- **Mammogram:** should be performed with any persistent palpable mass or other suspicious changes in the breast (e.g., bloody nipple discharge, skin retraction). A 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 possible biopsy are indicated.
- **Ultrasound:** most helpful to distinguish cystic and solid masses; useful initial test in younger women when simple cyst suspected.
- **Needle aspiration:** for cystic lesion; fluid can be discarded if clear and if mass disappears; otherwise send fluid for cytology, and biopsy may be needed.
- **Biopsy:** indicated in cases of dominant mass (even with normal mammographic findings) or suspicious nonpalpable mammographic findings.

D. DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

- **Fibrocystic change:** Typically found among women who are 30–50 yr old. Fibrocystic changes usually present as breast nodularity associated with cyclic bilateral pain or tenderness, which is worse premenstrually. Breast engorgement, increased density, and cyst formation are common and vary with menstrual cycle phase. The pain/discomfort associated with this condition can be relieved 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 a day) and decrease in caffeine consumption. Oral contraceptives are known to decrease benign breast disease. The appearance of a persistent dominant mass requires biopsy.
- **Benign breast tumor:** Most frequently diagnosed benign tumors of the breast are fibroadenomas, usually found in women aged 20–35. Typically, most masses are about 2–3 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. Definitive diagnosis is established by means of biopsy. A fibroadenoma may simply be observed; however, a large, growing, or otherwise suspicious mass should be surgically excised.
- **Breast cancer:** Incidence of breast cancer increases with age; risk factors include 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. Definitive diagnosis is established by means of biopsy, and referral to a surgeon is indicated. Although only a few cases of breast cancer have been reported among HIV-positive women, the unusual clinical presentations that have been noted, together with the rapid progression of disease that has been observed, have been suggestive of a “more virulent” course in the setting of HIV infection (Guth, 1999).

XIII. MENOPAUSE

As HIV-positive women live longer and more women nearing menopause or postmenopausal become infected, menopausal issues become more important to consider and address. To date, there has been no documented association between HIV disease and premature ovarian failure.

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 and in the United States averages between 51 and 52 yr of age. Certain medical conditions, such as osteoporosis and cardiovascular disease, have been linked to estrogen deficiency; associations have also been proposed between menopause and Alzheimer's disease and colon cancer (Hurd, 1996; Mishell, 1997b).

A. HISTORY

Last menstrual period and recent menstrual pattern (cycle length, duration, and amount of flow); any irregular or intermenstrual bleeding or spotting; hot flashes; genitourinary dryness/atrophy; decreased libido; anxiety, irritability, sleep disturbances, and depression; difficulty with memory; urinary symptoms

B. PHYSICAL EXAM

Vagina appears smoother in contour, "drier"; may be more easily traumatized and more vulnerable to infection.

C. EVALUATION

If indicated, confirmation of menopause can be provided by an elevated serum follicle-stimulating hormone level and a low estradiol level.

D. MANAGEMENT

■ Hormone Replacement Therapy (HRT)

The benefits and risks associated with HRT have been extensively studied among women who are HIV-negative. HRT is known to ameliorate symptoms of vasomotor instability (e.g., hot flashes, sleep disturbances, irritability, etc.) and urogenital atrophy (e.g., vaginal dryness, dyspareunia, etc.). More importantly, HRT is protective against cardiovascular disease and osteoporosis. Additional beneficial effects have been suggested with regards to prevention of Alzheimer's disease and colon cancer. One recent report found a trend toward increased survival among HIV-positive women on HRT and recommended that "HRT should be considered in the management of postmenopausal HIV-infected women who do not have an established contraindication as part of standard of care because of the documented known benefits among non-HIV-infected women" (Clark, 1997).

In addition to HRT, adequate calcium intake (1200 mg/day for menopausal women taking HRT; 1500 mg/day for women not on HRT) and the regular performance of weight-bearing exercise are important for bone protection.

Oral HRT can be administered in a continuous or cyclic fashion. The most commonly prescribed regimens are:

- Continuous therapy: Conjugated estrogens 0.625 mg po and medroxyprogesterone acetate 2.5–5 mg po once daily (available in combined formulations).
- Cyclic therapy: Conjugated estrogens 0.625 mg po once daily and medroxyprogesterone acetate 5–10 mg po once daily for 12–14 days per month.

Commonly used estrogen and progestin preparations are shown in Table 6–11 (ACOG, 1998).

TABLE 6-11: COMMONLY USED ESTROGEN AND PROGESTIN PREPARATIONS

<i>ESTROGEN PREPARATIONS*</i>	<i>PROGESTIN PREPARATIONS†</i>
Oral conjugated estrogen 0.625 mg	Medroxyprogesterone acetate 10 mg
Oral micronized estradiol 1 mg	Norethindrone 0.35 mg
Transdermal estradiol 0.05 mg/day	Micronized progesterone 200 mg
Oral esterified estrogen 0.625 mg	Progesterone vaginal suspension 90 mg
Estradiol vaginal ring	
* Doses listed (with exception of vaginal ring) are approximately equivalent in terms of relative potency.	
† Doses listed are approximately equivalent in terms of relative potency, with exception of norethindrone (approximately 0.5 relative potency).	

The most common side effects associated with hormone replacement regimens are irregular vaginal bleeding and breast tenderness. There is an increased risk of endometrial cancer in women treated with estrogen-only hormone replacement. The addition of progestin to the regimen either cyclically or continuously (in women with a uterus) protects the endometrium and prevents the development of hyperplasia and cancer. There is a small increase in the risk of venous thromboembolism in women on HRT. The issue of the effects that HRT may have on the development of breast cancer remains controversial; although some studies have demonstrated an increase in risk that may be related to the duration of hormone replacement, other studies have found no increase in risk. Contraindications to HRT include undiagnosed genital bleeding, active liver disease, recent myocardial infarction, active or prior history of thromboembolic disease, and breast or endometrial cancer.

■ Alternatives to HRT

- Progestin-only regimens (medroxyprogesterone acetate 10–30 mg or norethindrone 1–5 mg daily) may help relieve hot flashes in women who cannot or do not want to take estrogen-containing regimens.

- Nonhormonal lubricants and/or moisturizers or Estring (vaginal ring with estradiol reservoir that is changed every 90 days — minimal systemic absorption) for the management of urogenital atrophy.
- Bisphosphonates (e.g., fosamax) for the prevention or treatment of osteoporosis.
- Selective estrogen receptor modulators (Raloxifene 60 mg po every day) offer bone and cardiovascular benefit without evidence of breast or endometrial stimulation; no effect on hot flashes, small increase in risk of venous thromboembolism.

XIV. HEALTH MAINTENANCE ISSUES (Hilliard, 1996)

- **Gynecologic evaluation:** annually and as indicated by presence of symptoms, follow-up of ongoing problems, exposure to STDs, development of abnormal Pap smear, or other need for referral based on primary care evaluation
- **Pap smears:** twice within the first year of diagnosis and then annually; more frequent screening indicated with history of abnormal Pap, HPV infection, after treatment for cervical dysplasia, and with symptomatic HIV disease
- **STD screening:**
 - annual syphilis screening or with development of neurologic signs/symptoms
 - gonorrhea/chlamydia screening: offer annually at time of routine gynecologic visit; perform as indicated by the presence of relevant symptoms or findings on exam, with recent change in sexual partners, history of STD in sexual partner, periodically as indicated by sexual practices (commercial sex workers, multiple partners, inconsistent use of condoms), or with patient request
- **Mammography:** baseline at 35–40 yr; then every 1–2 yr until age 50, then annually; women at increased risk (first-degree family member(s) with breast cancer) should have annual screening after 40. Mammogram should be performed with presence of persistent palpable mass or other suspicious findings on exam
- **Sigmoidoscopy/colonoscopy:** sigmoidoscopy every 3–5 yr after age 50; colonoscopy in women at increased risk (first-degree family member with colorectal cancer) every 3–5 yr after age 40 or earlier with certain conditions (ulcerative colitis, familial polyposis, personal history of colon cancer)

XV. GUIDELINES FOR GYNECOLOGIC REFERRAL

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

- Uncertain diagnosis with gynecologic condition part of differential diagnosis
- Diagnosis of pregnancy
- Inadequate response to standard treatment regimens for gynecologic conditions
- Possible need for surgical intervention
- A premalignant or malignant condition is suspected

REFERENCES

- Adachi A, Fleming I, Burk RD, Ho GY, Klein RS. Women with human immunodeficiency virus and abnormal Papanicolaou smears: a prospective study of colposcopy and clinical outcome. *Obstet Gynecol* 81: 372-77, 1993.
- Ahdieh L, Munoz A, Vlahov D, Trimble C, Timpson L, Shah K. Cervical neoplasia and repeated positivity of human papillomavirus infection in human immunodeficiency virus-seropositive and -seronegative women. *Am J Epidemiol* 151: 1148-57, 2000.
- American College of Obstetricians and Gynecologists. *Cervical cytology: evaluation and management of abnormalities*. Technical Bulletin Number 183, August 1993.
- American College of Obstetricians and Gynecologists. *Hormone replacement therapy*. Educational Bulletin Number 247, May 1998.
- Anderson J, Clark RA, Watts DH, Till M, Arrastia C, Schuman P, et al. Idiopathic genital ulcers in women infected with human immunodeficiency virus. *J AIDS* 3: 343-7, 1996a.
- Anderson J, Cohen S, Kelly W, Shah K, Christensen C, Schuman P. Results of routine colposcopic examinations in women enrolled in the HIV epidemiology research study (HERS). *Int Conf AIDS* 11: 309 (Abst Tu.B.2255), Jul 7-12, 1996b.
- Augenbraun M, Feldman J, Chirgwin K, et al. Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. *Ann Intern Med* 123: 845-7, 1995.
- Barbosa C, Macasaet M, Brockmann S, Sierra MF, Xia Z, Duerr A. Pelvic inflammatory disease and human immunodeficiency virus infection. *Obstet Gynecol* 89: 65-70, 1997.
- Boardman L, Piepert J, Hogan J, Cooper A. Positive cone biopsy specimen margins in women infected with the human immunodeficiency virus. *Am J Obstet Gynecol* 181: 1395-9, 1999.
- Brown DR, Bryan JT, Cramer H, Katz BP, Handy V, Fife KH. Detection of multiple human papillomavirus types in condylomata acuminata from immunosuppressed patients. *J Infect Dis* 170: 759-65, 1994.
- Bukusi EA, Cohen CR, Stevens CE, et al. Effects of human immunodeficiency virus 1 infection on microbial origins of pelvic inflammatory disease and on efficacy of ambulatory oral therapy. *Am J Obstet Gynecol* 181: 1374-81, 1999.

- Calista D, Boschini A, Landi G. Resolution of disseminated molluscum contagiosum with Highly Active Anti-Retroviral Therapy (HAART) in patients with AIDS. *Eur J Dermatol* 9: 211–3, 1999.
- Cassone A, DeBernardis F, Torosantucci A, Tacconelli E, Tumbarello M, Cauda R. In: vitro and in vivo anticandidal activity of human immunodeficiency virus protease inhibitors. *J Infect Dis* 180: 448–53, 1999.
- Centers for Disease Control and Prevention. 1998 Guidelines for treatment of sexually transmitted diseases. *MMWR* 47: 1–116, 1998.
- Centers for Disease Control and Prevention. U.S. HIV and AIDS cases reported through December 1999. *HIV/AIDS Surveillance Report*, Vol. 11, No. 2, year-end edition, 1999.
- Chiasson MA. Declining AIDS mortality in New York City. New York City Department of Health. *Bull NY Acad Med* 74: 151–2, 1997a.
- Chiasson M, Ellerbrock TV, Bush TJ, Sun XW, Wright TC. Increased prevalence of vulvovaginal condyloma and vulvar intraepithelial neoplasia in women infected with the human immunodeficiency virus. *Obstet Gynecol* 89: 690–4, 1997b.
- Chirgwin K, Feldman J, Augenbraun M, Landesman S, Minkoff H. Incidence of venereal warts in human immunodeficiency virus-infected and uninfected women. *J Infect Dis* 172: 235–8, 1995.
- Chirgwin KD, Feldman J, Muncyirici-Delale O, et al. Menstrual function in Human Immunodeficiency Virus-infected women without Acquired Immunodeficiency Syndrome. *J Acquir Immune Defic Syndr Hum Retrovirol* 12: 489–94, 1996.
- Clark RA, Bessinger R. Clinical manifestations and predictors of survival in older women infected with HIV. *J Acquir Immune Defic Syndr Hum Retrovirol* 15: 341–5, 1997.
- Cohen CR, Sinei S, Reilly M, Bukusi E, et al. Effect of human immunodeficiency virus type 1 infection upon acute salpingitis: a laparoscopic study. *J Infect Dis* 178: 1352–8, 1998.
- Cu-Uvin S, Hogan JW, Warren D, et al. Prevalence of lower genital tract infections among human immunodeficiency virus (HIV)-seropositive and high risk HIV-seronegative women. HIV Epidemiology Research Study Group. *Clin Infect Dis* 29: 1145–50, 1999.
- Delmas M-C, Larsen C, vanBenthem B, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence, and regression. *AIDS* 14: 1775–84, 2000.
- Draper D, Donohoe W, Mortimer L, Heine RP. Cysteine proteases of *Trichomonas vaginalis* degrade secretory leukocyte protease inhibitor. *J Infect Dis* 178: 815–19, 1998.
- Droegemueller W. Benign gynecologic lesions. In: Mishell DR, Stenchever MA, Droegemueller W, Herbst AL, eds. *Comprehensive Gynecology*, 3rd ed. St. Louis: Mosby, 1997.
- Duerr A, Jamieson D, Cu-Uvin S, et al. The effect of highly active antiretroviral therapy on Pap smear abnormalities. XIII International AIDS Conference, Durban, South Africa (AbstMoPeB2245), July 9–14, 2000.
- Duerr A, Shah K, Schuman P, Klein RS, Cu-Uvin S. The effect of highly active antiretroviral therapy (HAART) on cervical dysplasia and HPV infection among HIV-infected women. *Int Conf AIDS* 12: 1052 (abst 60289), 1998.
- Duska LR, Flynn CF, Chen A, Whall-Strojwas D, Goodman A. Clinical evaluation of atypical glandular cells of undetermined significance on cervical cytology. *Obstet Gynecol* 91: 278–82, 1998.

- Ellerbrock TV, Wright TC, Bush TJ, et al. Characteristics of menstruation in women infected with human immunodeficiency virus. *Obstet Gynecol* 87: 1030-4, 1996.
- Ellerbrock TV, Chiasson MA, Bush TJ, et al. Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA* 282: 1031-7, 2000.
- El-Sadr W, Schuman P, Peng G, Capps L, Neaton J. Predictors of mucosal candidiasis among HIV-infected women. *Nat Conf Women HIV*: 107 (Abst 103.3), May 4-7, 1997.
- Evander M, Edlund K, Gustafsson A, et al. Human papillomavirus infection is transient in young women: a population-based cohort study. *J Infect Dis* 171: 1026-30, 1995.
- Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK, St. Louis ME. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 337: 1105-11, 1997.
- Fruchter R, Maiman M, Sedlis A, Bartley L, Camilien L, Arrastia CD. Multiple recurrences of cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Obstet Gynecol* 87: 338-44, 1996.
- Frankel RE, Selwyn PA, Mezger J, Andrews S. High prevalence of gynecologic disease among hospitalized women with human immunodeficiency virus infection. *Clin Infect Dis* 25: 706-12, 1997.
- Garzetti GG, Ciavattini A, Butini L, Vecchi A, Montroni M. Cervical dysplasia in HIV-seropositive women: role of human papillomavirus infection and immune status. *Gynecol Obstet Invest* 40: 52-6, 1995.
- Giannacopoulos KC, Hatzidaki EG, Papanicolaou NC, Relakis KJ, Kokori HG, Giannacopoulos CC. Genital tuberculosis in a HIV-infected woman: a case report. *Eur J Obstet Gynecol Reprod Biol* 80: 227-9, 1998.
- Giovanna O, Signori R, Fasolo MM, Schiavini M, Casella A, Gargnel A. Impact of HAART on clinical evolution of genital warts in HIV-positive patients. *Int Conf AIDS* 12: 301 (Abst 22192), 1998.
- Greenblatt RM, Bacchetti P, Barkan S, et al. Lower genital tract infections among HIV-infected and high-risk uninfected women: findings of the Women's Interagency HIV Study (WIHS). *Sex Transm Dis* 26: 143-51, 1999.
- Guth AA. Breast cancer and HIV: what do we know? *Am Surg* 65: 209-11, 1999.
- Heard I, Schmitz V, Costagliola D, Orth G, Kazatchkine MD. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *AIDS* 12: 1459-64, 1998.
- Heng M, Heng S, Allen S. Coinfection and synergy of human immunodeficiency virus-1 and herpes simplex virus. *Lancet* 343: 255-8, 1994.
- Hillemanns P, Ellerbrock TV, McPhillips S, et al. Prevalence of anal cytologic abnormalities and anal human papillomavirus infections in HIV-seropositive women. *AIDS* 10: 1641-7, 1996.
- Hillard PA. Preventive health care and screening. In: Berek JS, ed. *Novak's Gynecology*, 12th ed. Baltimore: Williams & Wilkins, 1996.
- Ho GH, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 338: 423-8, 1998.
- Hoegsberg B, Abulafia O, Sedlis A, et al. Sexually transmitted diseases and human immunodeficiency virus infection among women with pelvic inflammatory disease. *Am J Obstet Gynecol* 163: 1135-9, 1990.
- Holcomb K, Abulafia O, Matthews RP, et al. The significance of ASCUS cytology in HIV-positive women. *Gynecol Oncol* 75: 118-21, 1999a.

- Holcomb K, Matthews RP, Chapman JE, et al. The efficacy of cervical conization in the treatment of cervical intraepithelial neoplasia in HIV-positive women. *Gynecol Oncol* 74: 428–31, 1999b.
- Hook EW, Hansfield HH. Gonococcal infections in the adult. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. *Sexually Transmitted Diseases*, 3rd ed. New York: McGrawHill, 1999.
- Hurd WW. Menopause in: *Novak's Gynecology*, 12th Edition (Berek JS, ed.). Baltimore: Williams & Wilkins, 1996.
- Jacobson JM, Greenspan JS, Spritzler J, et al. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. National Institutes of Allergy and Infectious Diseases AIDS Clinical Trials Group. *N Engl J Med* 336: 1487–93, 1997.
- Jacobson JM, Spritzler J, Fox L, et al. Thalidomide for the treatment of esophageal aphthous ulcers in patients with human immunodeficiency virus infection. National Institutes of Allergy and Infectious Disease AIDS Clinical Trials Group. *J Infect Dis* 180: 61–7, 1999.
- Kamenga MC, De Cock KM, St Louis ME, et al. The impact of human immunodeficiency virus infection on pelvic inflammatory disease: a case-control study in Abidjan, Ivory Coast. *Am J Obstet Gynecol* 172: 919–25, 1995.
- Keller J, Sewell C, Anderson J. Incidence of recurrent cervical dysplasia in HIV-positive women after cervical excisional treatment. XIII International AIDS Conference, Durban, South Africa (Abst MoOrB237), July 9–14, 2000.
- Kennedy AW, Salmieri SS, Wirth SL, Biscotti CV, Tuason LJ, Travarca MJ. Results of the clinical evaluation of atypical glandular cells of undetermined significance (AGCUS) detected on cervical cytology screening. *Gynecol Oncol* 63: 14–8, 1996.
- Kerr-Layton JA, Stamm CA, Peterson LS, McGregor JA. Chronic plasma cell endometriosis in hysterectomy specimens of HIV-infected women: a retrospective analysis. *Infect Dis Obstet Gynecol* 6: 186–90, 1998.
- Klevens RM, Fleming PL, Mays MA, Frey R. Characteristics of women with AIDS and invasive cancer. *Obstet Gynecol* 88: 269–273, 1996.
- Korn AP, Abercrombie PD, Foster A. Vulvar intraepithelial neoplasia in women infected with human immunodeficiency virus-1. *Gynecol Oncol* 61: 384–6, 1995.
- Korn AP, Judson PL, Zaloudek CJ. Importance of atypical glandular cells of uncertain significance in cervical cytologic smears. *J Reprod Med* 43: 774–8, 1998.
- Korn A, Landers DV, Green JR, Sweet RL. Pelvic inflammatory disease in human immunodeficiency virus-infected women. *Obstet Gynecol* 82: 765–8, 1993.
- Li RK, Frankel R, Kirkpatrick WR, et al. Mycology, molecular epidemiology, and drug susceptibility of yeasts from vulvo-vaginal candidiasis in HIV-infected women. *Am Soc Microbiol* 97: 270 (Abst F63) May 4–8, 1997.
- Lomalisa P, Smith T, Guidozzi F. Human immunodeficiency virus infection and invasive cervical cancer in South Africa. *Gynecol Oncol* 77: 460–3, 2000.
- Luque AE, Demeter LM, Reichman RC. Association of human papillomavirus infection and disease with magnitude of human immunodeficiency virus type 1 (HIV-1) RNA plasma level among women with HIV-1 infection. *J Infect Dis* 179: 1405–9, 1999.
- Maiman M, Fruchter RG, Serur E, Remy JC, Feuer G, Boyce J. Human immunodeficiency virus infection and cervical neoplasia. *Gynecol Oncol* 38: 377–82, 1990.
- Maiman M, Fruchter RG, Guy L, Cuthill S, Levine P, Serur E. Human immunodeficiency virus infection and invasive cervical carcinoma. *Cancer* 71: 402–6, 1993.

- Maiman M. Management of cervical neoplasia in human immunodeficiency virus-infected women. *J Natl Cancer Inst Monogr* 23: 43–9, 1998.
- Maiman M, Watts DH, Andersen J, Clax P, Merino M, Kendall MA. Vaginal 5-fluorouracil for high-grade dysplasia in human immunodeficiency virus infection: a randomized trial. *Obstet Gynecol* 94: P954–61, 1999.
- Manos MM, Kinney WK, Hurley LB, Sherman ME, Shieh-Ngai J, Kurman RJ, et al. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA* 281: 1605–10, 1999.
- Martin HL, Richardson BA, Nyange PM et al. Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. *J Infect Dis* 180: 1863–68, 1999.
- Minkoff H, Feldman J, DeHovitz J, Landesman S, Burk R. A longitudinal study of human papillomavirus carriage in human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women. *Am J Obstet Gynecol* 178: 982–6, 1998.
- Minkoff HL, Eisenberger-Matityahu D, Feldman J, Burk R, Clarke L. Prevalence and incidence of gynecologic disorders among women infected with human immunodeficiency virus. *Am J Obstet Gynecol* 180: 824–36, 1999.
- Mishell DR. Abnormal uterine bleeding. In: Mishell DR, Stenchever MA, Droegemueller W, Herbst AL, eds. *Comprehensive Gynecology*, 3rd ed. St. Louis: Mosby, 1997a.
- Mishell DR. Menopause. In: Mishell DR, Stenchever MA, Droegemueller W, Herbst AL, eds. *Comprehensive Gynecology*, 3rd ed. St. Louis: Mosby, 1997b.
- Mostad SB, Kreiss JK, Ryncarz AJ, et al. Cervical shedding of herpes simplex virus in human immunodeficiency virus-infected women: effects of hormonal contraception, pregnancy, and vitamin A deficiency. *J Infect Dis* 181: 58–63, 2000.
- National Cancer Institute Workshop. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. *JAMA* 262: 931–4, 1989.
- Neary B, Young SB, Reuter KL, Cheeseman S, Savarese D. Ovarian Burkitt lymphoma: pelvic pain in a woman with AIDS. *Obstet Gynecol* 88: 706–8, 1996.
- Nielsen H. Hypermenorrhea associated with ritonavir. *Lancet* 353: 811–12, 1999.
- Olinger GG, Hashemi FB, Sha BE, Spear GT. Association of indicators of bacterial vaginosis with a female genital tract factor that induces expression of HIV-1. *AIDS* 13: 1905–12, 1999.
- Palefsky JM, Minkoff H, Kalish LA et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high risk HIV-negative women. *J Natl Cancer Inst* 91: 226–36, 1999.
- Petry KU, Kochel H, Bode U et al. Human papillomavirus is associated with the frequent detection of warty and basaloid high-grade neoplasia of the vulva and cervical neoplasia among immunocompromised women. *Gynecol Oncol* 60: 30–4, 1996.
- Petry KU, Bohmer G, Iftner T, Femming P, Stoll M, Schmidt RE. Human papillomavirus testing in primary screening for cervical cancer of human immunodeficiency virus-infected women, 1990-1998. *Gynecol Oncol* 75: 427–31, 1999.
- Phelps R, Smith DK, Gardner L, et al. Incidence of lung and invasive cervical cancer in HIV-infected women. XIII International AIDS Conference, Durban, South Africa (Abst TuPeB3168), July 9–14, 2000.
- Reyes M, Graber J, Reeves W. Acyclovir-resistant HSV: preliminary results from a national surveillance system. Abstract presented at International Conference on Emerging Infectious Diseases; March 10, 1998, Atlanta, Georgia.

- Rojansky N, Anteby SO. Gynecological neoplasias in the patient with HIV infection. *Obstet Gynecol Surv* 51: 679-83, 1996.
- Schuman P, Capps L, Peng G, et al. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection. A randomized, double-blind, placebo-controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. *Ann Intern Med* 126: 689-96, 1997a.
- Schuman P, Sobel J, Ohmit S, Mayer K, Klein R, Rompalo A, et al. Fluconazole resistance among oral and vaginal *Candida* isolates, the HER study. Natl Conf Women HIV107 (Abst 103.2), 1997b.
- Schuman P, Sobel J, Ohmit SE, et al. Mucosal candidal colonization and candidiasis in women with or at risk for human immunodeficiency virus infection. HIV Epidemiology Research Study (HERS). *Clin Infect Dis* 27: 1161-7, 1998.
- Schlesinger I, Oelrich DM, Tyring SK. Crusted (Norwegian) scabies in patients with AIDS: the range of clinical presentations. *South Med J* 87: 352-6, 1994.
- Sewell C, Keller J, Anderson J. Immunologic, virologic, and histologic correlates of ASCUS/LSIL and progression in HIV-positive women. XIII International AIDS Conference, Durban, South Africa (Abst MoPeB2228), July 9-14, 2000.
- Shah KV, Munoz A, Klein RS, et al. Prolonged persistence of genital human papillomavirus infections in HIV-infected women. Int Conf AIDS 11: 345 (Abst Tu.C.2466), July 7-12, 1996.
- Shah PN, Smith JR, Wells C, et al. Menstrual symptoms in women infected by the human immunodeficiency virus. *Obstet Gynecol* 83: 397-400, 1994.
- Six C, Heard I, Bergeron C, et al. Comparative prevalence, incidence and short-term prognosis of cervical squamous intraepithelial lesions amongst HIV-positive and HIV-negative women. *AIDS* 12: 1047-56, 1998.
- Sloand EM, Klein HG, Banks SM, Varelzdis B, Merritt S, Pierce P. Epidemiology of thrombocytopenia in HIV infection. *Eur J Haematol* 48: 168-72, 1992.
- Sobel J. Chapter on treating candida. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. *Sexually Transmitted Diseases*, 3rd ed. New York: McGrawHill, 1999.
- Sorvillo F, Kovacs A, Kerndt P, Stek A, Munderspach L, Sanchez-Keeland L. Risk factors for trichomoniasis among women with human immunodeficiency virus (HIV) infection at a public clinic in Los Angeles County, California: implications for HIV prevention. *Am J Trop Med Hyg* 58: 495-500, 1998.
- Sperling RS, Friedman F, Joyner M, Brodman M, Dottino P. Seroprevalence of human immunodeficiency virus in women admitted to the hospital with pelvic inflammatory disease. *J Reprod Med* 36: 122-4, 1991.
- Spinillo A, Capuzzo E, Tenti P, De Santolo A, Piazzzi G, Iasci A. Adequacy of screening cervical cytology among human immunodeficiency virus seropositive women. *Gynecol Oncol* 69: 109-13, 1998.
- Stamm WE. Chlamydia trachomatis infections of the adult. In: Holmes KK, Sparling PF, Mardh P-A, et al, eds. *Sexually Transmitted Diseases*, 3rd ed. New York: McGrawHill, 1999.
- Sun XW, Ellerbrock TV, Lungu O, Chiasson MA, Bush TJ, Wright TC. Human papillomavirus infection in HIV-seropositive women. *Obstet Gynecol* 85: 680-6, 1995.
- Sun XW, Kuhn L, Ellerbrock TV, Chiasson MA, Bush TJ, Wright TC. Human papillomavirus infection in women infected with the human immunodeficiency virus. *N Engl J Med* 337: 1343-9, 1997.

- Uberti-Foppa C, Origoni M, Maillard M, et al. Evaluation of the detection of human papillomavirus genotypes in cervical specimens by hybrid capture as screening for precancerous lesions in HIV-positive women. *J Med Virol* 56: 133–7, 1998.
- Weber T, Chin K, Sidhu JS, Janssen RS. Prevalence of invasive cervical cancer among HIV-infected and uninfected hospital patients, 1994–1995. Abst 717. Presented at the 5th Conference on Retroviruses and Opportunistic Infections. Chicago, IL, 1998.
- Williams A, Darragh TM, Vranizan K, Ochia C, Moss AR, Palefsky JM. Anal and cervical human papillomavirus infection and risk of anal and cervical epithelial abnormalities in human immunodeficiency virus-infected women. *Obstet Gynecol* 83: 205–11, 1994.
- Wright TC, Moscarella RD, Dole P, Ellerbrock TV, Chiasson MA, Vandevanter N. Significance of mild cytologic atypia in women infected with human immunodeficiency virus. *Obstet Gynecol* 87: 515–19, 1996a.
- Wright T, Sun XW. Anogenital papillomavirus infection and neoplasia in immunodeficient women. *Obstet Gynecol Clin North Am* 23: 861–93, 1996b.