MENSTRUAL DISORDERS IN HIV-INFECTED WOMEN

I. INTRODUCTION

Initial studies in the 1990s that examined differences in menstrual function between HIV-infected and non-HIV-infected women showed conflicting results. More carefully controlled studies since that time have not revealed significant differences in menstrual disorders between HIV-infected and non-HIV-infected women.[1] Differences in rates of dysmenorrhea or perimenopausal symptoms have also not been demonstrated. However, some differences in rates of amenorrhea and oligomenorrhea have been found between HIV-infected women with advanced disease and non-HIV-infected women.[2,3]

The relationship between HIV infection and early menopause (occurring before age 40) has not yet been established in clinical studies. This is a key concern because of the metabolic changes associated with menopause, such as decreased bone density and increased cardiovascular risk.[4,5] For more information about menopause, see *Medical Care for Menopausal and Older Women With HIV Infection*. Additional information regarding effects of antiretroviral therapy (ART) can be found in *Long-Term Complications of Antiretroviral Therapy*.

As with non-HIV-infected women, abnormal vaginal bleeding should raise concerns about the possibility of pregnancy or gynecologic disorders such as ectopic pregnancy, uterine fibroids, genital tract neoplasm, or coagulopathy.

II. CAUSES OF ABNORMAL MENSES IN HIV-INFECTED WOMEN

Several chronic conditions and diseases associated with menstrual irregularities are more prevalent in HIV-infected women than in the general population.[6,7] Common causes of menstrual irregularities in HIV-infected women are shown in Table 1. Determining whether HIV has directly affected menstrual function is complicated by the frequency of these conditions and diseases in all women. In addition, several epidemiological factors that are associated with amenorrhea or early onset of menopause, including smoking, poor nutritional status, lower socioeconomic status, and emotional stress, are also more prevalent in HIV-infected women than in the general population.[1,7]

Key Point:

- HIV-specific causes of abnormal uterine bleeding (AUB) are unusual.
- Many studies have demonstrated that comorbidities are more likely to be the cause of menstrual abnormalities in HIV-infected women than HIV itself.[7]

High rates of amenorrhea for reasons other than menopause have been observed in some, but not all, studies of HIV-infected women. Identification of the cause of this type of amenorrhea may be important for determining appropriate management of postmenopausal conditions such as lipid and cardiac abnormalities and osteoporosis.[1,8]

Abnormal vaginal bleeding is a common symptom of cervical cancer. Cervical cytology tests (Pap tests) screen for cervical abnormalities but do not adequately screen for endometrial neoplasms. A negative Pap test result does not exclude the possibility of neoplasia. HIV-infected women with negative Pap test results but continued abnormal bleeding should be evaluated and managed in the same manner as non-HIV-infected women.

Protease inhibitors have been linked to increased bleeding in some individuals, but this association has only been well established for hemophiliacs.[9] In general, studies have shown that women receiving ART have fewer menstrual abnormalities than immunocompromised HIV-infected women who are not receiving ART. In one study, both a longer time receiving ART and higher CD4 cell counts were associated with less likelihood of amenorrhea.[2]

TABLE 1
CAUSES OF MENSTRUAL IRREGULARITIES

Gynecologic Causes	Non-gynecologic Causes
• Pregnancy, ectopic pregnancy, miscarriage • Polycystic ovarian syndrome (PCOS) • Ovarian insufficiency – premature ovarian failure • Cervical polyps, cervicitis • Endometrial conditions • Pelvic inflammatory disease (PID) • Uterine fibroids • Sexually transmitted infections (STIs) • Certain cancers ◦ Endometrial ◦ Cervical ◦ Vulvar ◦ Vaginal	• Stress • Excess exercise • Eating disorders • Thyroid/pituitary disease • Adrenal disease • Wasting, weight loss, or low BMI • Chronic diseases ◦ Diabetes ◦ Kidney disease ◦ Liver disease ◦ Inflammatory bowel disease ◦ Immune suppression • Medications ◦ Anticoagulants ◦ Psychotropics, phenytoin ◦ Narcotic analgesics ◦ Methadone, heroin ◦ Corticosteroids ◦ Hormonal therapies ◦ Herbal supplements with estrogenic activity ◦ Protease inhibitors

III. Assessing Menstrual Irregularity in HIV-Infected Women

Recommendations:

Clinicians should obtain a complete menstrual history in all HIV-infected female patients that includes the following: (AIII)

- **Age of onset of menses**
- **Amount, duration, and frequency of menses or vaginal bleeding**
- **Recent changes in the menstrual cycle (during the past 6 to 12 months)**
- **Whether the onset of menstrual irregularity was associated with pain, intercourse, weight change, contraception, or new medications**

When evaluating amenorrhea and other menstrual irregularities in HIV-infected women, clinicians should review the patient's disease status, including the presence of opportunistic infections, and inquire about substance use and use of medications, such as psychotropics, that contribute to abnormal menses. (AIII)

Clinicians should obtain a pregnancy test for all HIV-infected women of childbearing potential who give a current history of amenorrhea or irregular vaginal bleeding, regardless of history of sexual activity or contraception use. Patients who are pregnant should be referred to an obstetrical HIV-experienced clinician for evaluation and management as soon as possible. (AIII)

Clinicians should obtain annual Pap tests for all HIV-infected women. *Pap tests should be repeated in patients with abnormal vaginal bleeding*. Follow-up would be determined by the results of the Pap test (see *Neoplastic Complications of HIV Infection*). (AIII)

Clinicians should instruct patients with abnormal uterine bleeding and no acute signs or symptoms to keep a 3-month calendar outlining their bleeding patterns. (AIII)

Key Point:

The most common reason for amenorrhea in premenopausal women is pregnancy. The onset of irregular bleeding, which may or may not be accompanied by pain, may indicate complications such as ectopic pregnancy, miscarriage, or incomplete abortion. Therefore, the first step in the evaluation and management of any change in menstrual pattern in women of childbearing potential should be a pregnancy test, even if the history suggests that pregnancy is unlikely.

Menses that vary in frequency, duration, or amount from what is considered to be a normal menstrual cycle for a given patient are considered irregular. The accepted terms for abnormal uterine bleeding are defined in Table 2. Because recall of menses has been shown to be unreliable, patients with menstrual irregularities and no acute signs or symptoms should be asked to keep an ongoing calendar outlining their menses/bleeding patterns for 3 months. The volume of blood loss is difficult to estimate so clinicians may ask about the number of tampons or pads used, how frequently the pads are changed, whether the pads/tampons are soaked through, and whether there are clots. Associated pains, fever, discharge, and urinary or rectal complaints should also be characterized and documented.

Pap tests do not adequately screen for all gynecologic cancers. HIV-infected women with negative Pap test results but continued abnormal bleeding should be evaluated and managed in the same manner as non-HIV-infected women.

TABLE 2 DEFINITIONS OF TERMS FOR ABNORMAL MENSTRUAL BLEEDING	
Condition	**Definition**
Amenorrhea	Cessation of bleeding for ≥3 months
Polymenorrhea	Menstrual bleeding occurs <21 days after prior menses
Oligomenorrhea	Menstrual bleeding occurs >35 days after prior menses
Menorrhagia/hypermenorrhea	Regular cycles with excessive flow (>80 ml) or duration (>7 days)
Metrorrhagia	Irregular bleeding or bleeding between periods ("breakthrough bleeding")
Menometrorrhagia	Bleeding that is both heavy and irregular
Post-menopausal bleeding	Bleeding >1 year after cessation of menses
Post-coital bleeding	Bleeding after intercourse
Mid-cycle spotting	Light bleeding around the time of ovulation

IV. MANAGING MENSTRUAL IRREGULARITIES IN HIV-INFECTED WOMEN

RECOMMENDATIONS:

Clinicians with gynecologic expertise should evaluate and manage menstrual irregularities in HIV-infected women in the same manner as non-HIV-infected women. The causes of menstrual abnormalities are unlikely to be HIV-related. (AIII)

Clinicians without gynecologic expertise should refer HIV-infected women with apparent menstrual irregularities without acute symptoms to a gynecologic care provider for evaluation and management. (AIII)

Clinicians should refer women with amenorrhea or irregular bleeding for immediate emergency evaluation when: (AII)

- **They present with pain**
- **They have a positive pregnancy test and pain**
- **Their vital signs are consistent with acute blood loss**

Key Point:
Ectopic pregnancy, spontaneous abortion (miscarriage), and other causes of uterine bleeding can result in either obvious or hidden blood loss. Symptoms of hypovolemia, such as pallor, hypotension, tachycardia, change in mental status, and paradoxical hypertension, may indicate a life-threatening condition and require immediate evaluation for blood loss that may not be evident.

All HIV-infected women with anovulatory bleeding or amenorrhea of unknown etiology should be referred to a gynecologic care provider with HIV expertise for diagnosis and treatment to ensure that the causes are appropriately identified and addressed.

REFERENCES

1. Cejtin HE, Kalinowski A, Bacchetti P, et al. Effects of human immunodeficiency virus on protracted amenorrhea and ovarian dysfunction. *Obstet Gynecol* 2006;108:1423-1431. [PubMed]

2. Massad LS, Evans CT, Minkoff H, et al. Effects of HIV infection and its treatment on self-reported menstrual abnormalities in women. *J Womens Health (Larchmt)* 2006;15:591-598. [PubMed]

3. Harlow SD, Schuman P, Cohen M, et al. Effect of HIV infection on menstrual cycle length. *J Acquir Immune Defic Syndr* 2000;24:68-75. [PubMed]

4. Kojic EM, Wang CC, Cu-Uvin S. HIV and menopause: A review. *J Womens Health (Larchmt)* 2007;16:1402-1411. Review. [PubMed]

5. Product insert. Viread (tenofovir). 2010. Gilead Sciences, 333 Lakeside Drive Foster City, CA. Available at: www.gilead.com/pdf/viread_pi.pdf

6. Grinspoon S, Corcoran C, Miller K, et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. *J Clin Endocrinol Metab* 1997;82:1332-1337. [PubMed]

7. Cejtin HE. Gynecologic issues in the HIV-infected woman. *Infect Dis Clin North Am* 2008;22:709-739, vii. Review. [PubMed]

8. Seifer DB, Golub ET, Lambert-Messerlian G, et al. Biologic markers of ovarian reserve and reproductive aging: Application in a cohort study of HIV infection in women. *Fertil Steril* 2007;88:1645-1652. [PubMed]

9. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. Available at: www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf