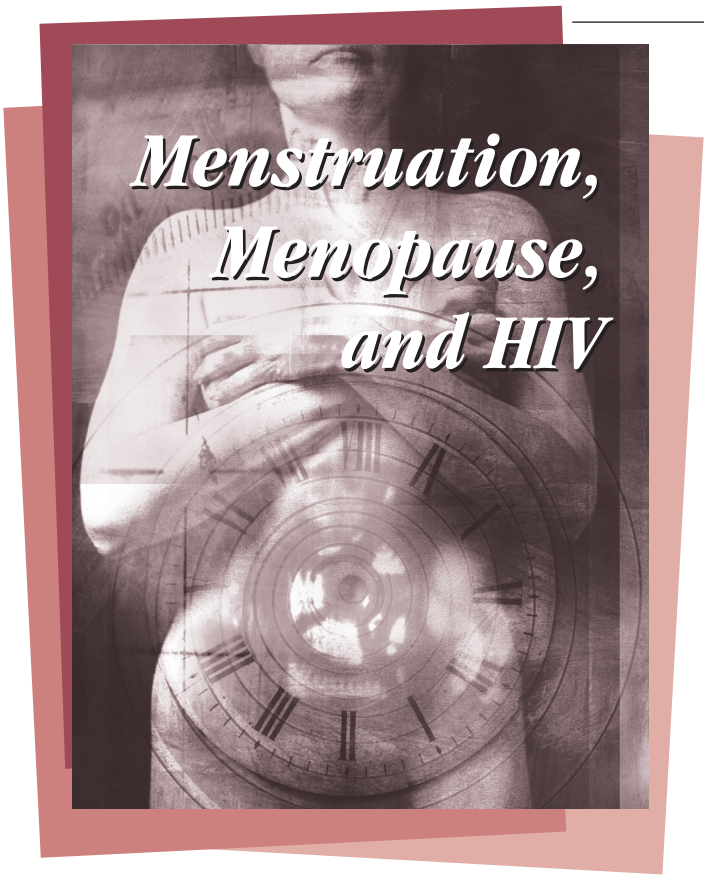

Menstruation, Menopause, and HIV

Anne Monroe, MD

There is a growing need for research about the effects of HIV on the menstrual cycle and menopause. HIV positive women and their care providers need to know what to expect at all life stages, and need strategies for optimal long-term care in the HAART era. Once the impact of HIV on menopause is better understood, clinical management can be individually tailored to avoid long-term complications such as osteoporosis and cardiovascular disease.

The Menstrual Cycle

There is a wide range of "normal" with regard to menstruation. A normal menstrual period ranges from two to six days, with an average length of four days. A mentrual cycle generally concludes in a period every 21 to 35 days, with an average loss of 40 mL of blood per period.

Normal menstruation is characterized by cyclic changes in the levels of hormones produced by the pituitary gland (luteinizing hormone [LH] and follicle stimulating hormone [FSH]) and by the ovaries (estrogen and progesterone). (See "HIV and Hormones" in the Summer 2004 issue of *BETA*.)

Menstrual irregularities are common in both HIV positive and HIV negative women. Amenorrhea is the absence of menstruation. Primary amenorrhea refers to a woman older than 16 years who has never menstruated, while secondary amenorrhea is the absence of menses for three to six months or longer in a woman who previously menstruated.

Menorrhagia refers to the loss of more than 80 mL of blood during each cycle of regular length, whereas dysfunctional uterine bleeding (DUB) is defined as loss of more than 80 mL of blood during irregular cycles; both menorrhagia and DUB may result in anemia, or reduced number of red blood cells. Dysmenorrhea refers to pain during menses, which may be a crampy discomfort with no underlying gynecologic condition, or may stem from endometriosis (growth of endometrium, or uterine lining tissue, outside of the uterus) or pelvic inflammatory disease (PID).

Many conditions can cause abnormal menstrual bleeding. Uterine fibroids may cause heavy or prolonged periods. Genital tract infections may cause abnormal bleeding, usually accompanied by other signs of infection, such as pain, vaginal discharge, or fever. Cancer in the genital tract (cervical cancer, endometrial cancer) may also cause bleeding. Other medical conditions, including thyroid abnormalities and low platelet counts, can interfere with regular menstrual cycles. Extreme

weight loss or being underweight can cause acquired gonadotropin releasing hormone deficiency, eliminating the stimulus for LH and FSH release and resulting in amenorrhea. Hormonal dysfunction that disrupts ovulation can also lead to abnormal bleeding, which may be more common in HIV positive women, although studies are inconclusive.

Use of drugs (including methadone) may interfere with hormonal regulation and cause abnormal bleeding. Some medications commonly used by HIV positive women, such as contraceptives and megestrol acetate (Megace), may also interfere with normal menstruation. Antiretroviral agents may also contribute to abnormal bleeding; for example, one case series reported heavy menstrual bleeding associated with full-dose ritonavir (Norvir) in a small sample of young women.

Menstrual Irregularities in Women with HIV

HIV positive women and their care providers should be aware of changes in the menstrual cycle that may be related to HIV and its treatment. Many studies have tried to sort out the effects of HIV on the menstrual cycle, with contradictory results. Much of the research on menstrual abnormalities in women with HIV/AIDS was conducted during the early years of the epidemic, when women more often had advanced disease accompanied by wasting. Menstrual irregularities in women on antiretroviral therapy with well-controlled HIV are less well understood.

In a study of the effect of HIV infection on menstrual cycle length, published in the May 2000 issue of the *Journal of Acquired Immune Deficiency Syndromes,* Sioban Harlow, PhD, and colleagues collected data from 802 HIV positive and 273 HIV negative women. The women completed monthly menstrual calendars and answered questions regarding antiretroviral therapy and recreational drug use. The researchers examined relationships between viral load and CD4 cell count and menstrual cycle length. Overall, HIV infection did not increase the likelihood of having a cycle longer than 40 days (i.e., a longer interval between periods). However, HIV positive women with more advanced immunosuppression (CD4 counts less than 200 cells/mm^3) were more likely to have long cycles. The researchers concluded that HIV serostatus had little effect on menstrual cycle length, and that other factors—for example, advanced disease, age, race, malnutrition, wasting, and substance use—were more important.

In an earlier study, Keith Chirgwin, MD, and colleagues evaluated 248 HIV positive and 82 demographically similar HIV negative women, and found that women with HIV were more likely to experience amenorrhea for more than three months and had intervals greater than six weeks between menstrual cycles. However, menstrual irregularities were not found to be significantly associated with HIV disease status in this study.

Tedd Ellerbrock, MD, and colleagues interviewed 197 HIV positive and 189 HIV negative women to assess the effect of HIV on menstruation. The researchers collected data retrospectively to identify trends in menstrual cycles over the previous year. The study found no major differences between the two groups, and no relationship between degree of immunosuppression and menstrual irregularities. However, the design of this study was not ideal, as it required that women recall characteristics

Tests for Diagnosing Menstrual Abnormalities

A full history and physical give the health-care practitioner clues to the underlying cause(s) of abnormal menstrual bleeding and directs all additional testing. These tests and screenings may include:

Blood tests

- Complete blood count (CBC) to screen for anemia, low platelet count
- Endocrine studies to check various hormone levels for abnormalities
- Coagulation studies to check blood clotting

Pelvic exam

- Collection of samples for sexually transmitted infection testing
- Pap smear to screen for cervical cancer
- Palpation of uterus and ovaries to check for abnormalities

Pelvic ultrasound (if indicated)

An ultrasound probe is inserted in the vagina to assess uterus size, presence of fibroids, thickness of the uterine lining, ovarian abnormalities, and presence of endometriosis.

Endometrial biopsy (if indicated)

A thin tube is inserted through the cervix into the uterus and samples from the endometrium (uterine lining) are collected to test for abnormalities, such as inflammation or cancer.

of their menstrual cycles for the entire year prior to the interview.

Wasting syndrome associated with HIV is known to affect the menstrual cycle, as also occurs in HIV negative women—such as athletes and malnourished women—who lose a significant percentage of body fat or lean body mass. For example, a small study by Steven Grinspoon, MD, and colleagues found that among 31 HIV positive women with varying degrees of wasting, 20% overall had experienced amenorrhea. Among the women with amenorrhea, muscle mass was significantly lower, as was the total level of estradiol (a form of estrogen). The study revealed a higher rate of amenorrhea in women with less than 90% of ideal body weight.

Menopause

Menopause is a natural, normal life stage. It is defined as the end of menses and is characterized by 12 months without a menstrual period. The hormonal changes associated with menopause include elevation of FSH and LH levels and decreased estrogen levels. In the United States, the final menstrual period occurs at an average age of 51 years. There is evidence supporting a younger age of menopause onset (48 years) in African-American women.

A diagnosis of menopause can be made in women over the age of 45 years who have stopped menstruating for at least one year. Menopause is a clinical diagnosis; no diagnostic tests are necessary. However, in younger women who stop menstruating and are not pregnant, hormone testing for premature ovarian failure should be performed.

Women beginning the menopausal transition (perimenopause) may have irregular cycles with either light or heavy bleeding. They may also experience hot flashes, a heat sensation that starts on the upper face or chest and can spread throughout the entire body. Hot flashes at night may be particularly troublesome if they disturb sleep. Another common symptom of menopause resulting from decreased estrogen production is vaginal thinning and dryness, which increase in prevalence as women age. Thinning of the vaginal wall may cause pain during sexual intercourse.

Other menopausal symptoms include breast pain or tenderness—more common during the early menopausal transition than in late menopause—and mood changes, such as depression. Other mood-related symptoms may include nervousness, irritability, and frequent mood fluctuations. Some women experience forgetfulness and impaired concentration. Long-term physiological changes associated with menopause include a higher risk of osteoporosis (bone thinning) and cardiovascular disease.

HIV and Menopause

As women with HIV live longer thanks to effective treatment, more research is needed on the interactions between HIV disease, antiretroviral therapy, and menopause. More than ever, HIV positive women need support and strategies for dealing with the changes of menopause. Considerable research has explored the relationship between menopause and HIV, but this too has yielded inconsistent results.

One large study examined the relationship between HIV disease and onset of menopause. Ellie Schoenbaum, MD, and colleagues examined the effects of HIV infection, HAART, street drug use, and immune status on age of onset of menopause. Their study group included 571 women, half of whom were HIV positive. Half the women in both the HIV positive and HIV negative groups used recreational drugs, and 90% were current or former smokers. About half were African-American, 40% were Latina, and 10% were white. In this population with high rates of drug use, the average age of menopause onset was 46 years in the HIV positive group and 47 years in the HIV negative group.

The likelihood of early menopause rose with increasing degree of immunosuppression. In women with CD4 counts less than 200 cells/mm^3, the mean age of onset of menopause was 42.5 years. Women with low levels of physical activity were also at risk for earlier onset of menopause. This study showed no association between low body mass index (BMI) or cigarette smoking and early onset of menopause, contrary to some other epidemiological studies. There was also no association observed in this study between HAART use and earlier onset of menopause.

Clearly, more research into the effect of HIV on onset of menopause is necessary. The HIV Menopause Clinic—the first of its kind in the U.S.—was founded by Susan Cu-Uvin, MD, director of the Miriam Hospital's Immunology Center in Providence, Rhode Island. The

Medications Used to Prevent or Reverse Osteoporosis

Bisphosphonates: alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)

Selective estrogen receptor modulators (SERMs): raloxifene (Evista), tamoxifen (Nolvadex)

clinic is currently collecting observational data as a first step toward large-scale research on menopause in HIV positive women.

In addition, numerous studies are underway to determine the effects of HIV infection and antiretroviral therapy on the risk of developing cardiovascular disease and osteoporosis. These effects may be compounded in HIV positive menopausal women on HAART.

Osteopenia and Osteoporosis

In the February 20, 2004, issue of *Acquired Immune Deficiency Syndromes,* Sara Dolan, NP, and colleagues report on a study comparing the risk of osteopenia—bone thinning, a precursor to osteoporosis (more severe bone atrophy)—in HIV positive and HIV negative women. They found that women with HIV were more likely to have osteopenia, even after controlling for age and BMI. Prior exposure to antiretroviral therapy did not appear to have any significant effect on bone density. The study also found that abnormal menstrual function was associated with lower bone density, and that women who maintained their baseline weight were more likely to maintain their bone mass, compared with those who had HIV-related wasting.

A study by Julia Arnsten, MD, and colleagues with the U.S. Menopause Study, published in the April 1, 2006, issue of *Clinical Infectious Diseases,* analyzed data from 263 HIV positive and 232 HIV negative women; the median age was 44, most were pre-menopausal, and roughly three-quarters were on HAART. Overall, the HIV positive women had lower bone mineral density (BMD) in their hips and lumbar spines: 27% of the HIV positive women had low BMD, versus 19% of the HIV negative participants.

Cardiovascular Risk

Post-menopausal women have an increased risk of cardiovascular disease as estrogen levels decrease. HIV positive people on antiretroviral therapy are also at increased risk of cardiovascular disease, as certain antiretroviral medications (especially protease inhibitors) can lead to elevations in low-density lipoprotein (LDL, or "bad") cholesterol and triglycerides. This side effect is quite common: multiple studies have shown that up to 20% of patients on HAART develop hyperlipidemia. Antiretroviral drugs may also cause insulin resistance and diabetes mellitus (impaired glucose tolerance), which in turn increase the risk of heart disease.

Management of Menopause

Although menopause is a natural process, many women seek medical assistance to manage the symptoms of menopause, both short-term symptoms such as hot flashes and vaginal dryness and more serious long-term complications such as elevated risk of osteoporosis and cardiovascular disease.

Not long ago, it was widely believed that hormone replacement therapy (HRT)—replacing estrogen, with or without the addition of progesterone—could safely alleviate

HEALTH SCREENING

Mammograms (breast cancer screening):
A mammogram is recommended every 1 to 2 years starting at age 40, then yearly after age 50. Monthly self-breast-exams are also advised.

Pap smears (cervical cancer screening):
HIV positive women should have two Pap smears during the first year following HIV diagnosis, then one per year thereafter.

Cholesterol checks:
For HIV positive people not on HAART, regular cholesterol checks should begin at age 45. Individuals at higher risk of heart disease (smokers, diabetics, or people with a family history of heart disease) should start cholesterol checks at age 20. Cholesterol should be checked before starting antiretroviral therapy, three to six months after starting therapy, and at least annually while on HAART.

Blood pressure checks:
Blood pressure checks are recommended at least once every two years.

menopausal symptoms while at the same time helping women avoid the detrimental long-term effects of reduced estrogen levels.

In recent years, however, data from large longitudinal studies have shown that the risks of HRT outweigh the benefits for many women. The Women's Health Initiative (WHI) is a group of studies designed to investigate long-term HRT. One study evaluated combined estrogen/progestin (synthetic progesterone) therapy versus placebo in more than 160,000 menopausal women, with an average follow-up period of more than five years.

In 2002, the estrogen/progestin arm of the study was discontinued after it was shown that women receiving long-term combination HRT had an increased risk of cardiovascular disease, cerebrovascular disease (stroke), deep vein thrombosis (blood clots), and breast cancer. The study did, however, reveal some beneficial effects associated with HRT: decreased rates of bone fractures and colon cancer. The estrogen-only arm of the study (which included women who had received hysterectomies and therefore were not at risk for uterine cancer) was later stopped after data showed that estrogen replacement did not reduce the risk of heart attack and slightly raised the risk of stroke.

Symptom Management

Acute symptoms often improve spontaneously as the hormonal fluctuations of perimenopause and early menopause level out. Women with severe hot flashes may find relief through short-term, low-dose estrogen/progestin HRT.

Alternatives to HRT for hot flashes include using a selective seratonin reuptake inhibitor (SSRI) antidepressant, most commonly venlafaxine (Effexor). Some women use soy products or herbal remedies such as black cohosh (*Cimicifuga racemosa*) or evening primrose (*Oenothera biennis*)—which contain estrogen-like compounds known as phytoestrogens—to alleviate hot flashes, bloating, and mood swings. Dr. Cu-Uvin notes that there is conflicting evidence from clinical trials about the effectiveness of herbal therapies, but for her patients who wish to try soy products, she recommends 40–80 mg of isoflavones taken daily for up to six months. (It is essential, however, for an HIV positive woman to consult with her own health-care provider before beginning a supplement regimen, as some herbal and dietary supplements can interact with antiretroviral medications and other drugs.)

One solution for vaginal dryness and thinning is the use of topical estrogen creams or lubricants during sexual intercourse. There is also an estrogen-releasing silicone ring (Estring) that can be inserted in the vagina and worn for three months at a time to alleviate the symptoms of vaginal atrophy. Local administration of estrogen is not associated with the same risks as systemic HRT.

Avoiding Long-Term Complications

One of the beneficial effects of HRT demonstrated in the WHI study was a decrease in the risk of bone fractures. However, there are other interventions that can decrease

TESTS FOR WOMEN

Colorectal cancer screening:
Testing for colorectal cancer (colonoscopy or flexible sigmoidoscopy) should start at age 50. If colonoscopy results are normal, repeat every ten years; if sigmoidoscopy results are normal, repeat every 5 years.

Diabetes tests:
A blood sugar test screens for diabetes. Patients on HAART should have a blood sugar test one to three months after starting therapy and then at least every three to six months.

Osteoporosis screening:
A bone density test to screen for osteoporosis is recommended for all women at age 65. Women may need to be tested earlier if they weigh less than 154 pounds, take chronic steroid therapy, are white or Asian, or smoke. There are currently no changes to these recommendations based on HIV status or HAART use; patients on HAART should talk to their health-care providers to determine whether an earlier test is indicated.

Sexually transmitted infection screening:
HIV positive women with multiple sex partners are advised to receive biannual screenings for syphilis, gonorrhea, and chlamydia, as these infections may be more serious for people with immunosuppression.

the danger of osteopenia and osteoporosis without the risks associated with HRT. Adequate dietary intake of calcium and vitamin D is extremely important—postmenopausal women need 1500 mg of calcium daily in addition to 400 units of vitamin D (800 units for women over age 70). Weight-bearing exercise also helps maintain bone mass. In addition, several medications can prevent and even reverse osteoporosis (see sidebar, page 41).

Similarly, there are many ways to reduce the risk of cardiovascular disease. The first step is lifestyle modification, including exercising, eating a low-fat diet, and quitting smoking. Statins—drugs such as atorvastatin (Lipitor) and simvastatin (Zocor)—reduce LDL cholesterol and triglyceride levels and can help lower the risk of heart disease. Other strategies include diabetes management and, for some people (and under their doctor's orders), taking a daily aspirin.

Conclusion

Knowledge regarding the menstrual cycle and menopause in HIV positive women has advanced since the beginning of the epidemic, but much remains to be learned. As women live longer with HIV, it is increasingly important to determine optimal care for a healthy menopause.

As with many aspects of HIV care, management of menopausal symptoms and complications should be tailored to the individual patient. Dr. Cu-Uvin notes that many of her patients have refused even short-term HRT due to their fear of complications, but estrogen replacement remains a viable option for some women, and the absolute risk of complications such as heart attacks and strokes remains small.

Until more is known, HIV positive women are advised to receive the recommended regular health check-ups for their age group (see sidebar, pages 42–43). Women should also discuss bothersome menstrual irregularities or menopause symptoms with their health-care providers and together explore individualized management strategies.

Anne Monroe, MD, is a resident in Internal Medicine at Jackson Memorial Hospital in Miami, Florida. She has a longstanding interest in HIV clinical trials and women's health.

Selected Sources

Abularach, S. and J. Anderson. Gynecologic problems. In *A Guide to the Clinical Care of Women with HIV.* Rockville, MD: U.S. Department of Health and Human Services, HRSA, HIV/AIDS Bureau. Pp. 177–81. 2005.

Arnsten, J. and others. HIV infection and bone mineral density in middle-aged women. *Clinical Infectious Diseases* 42:1014–20. April 1, 2006.

Bromberger, J. Prospective study of the determinants of age at menopause. *American Journal of Epidemiology* 145(2):124–33. January 15, 1997.

Cejtin, H. and others. Gynecologic issues in the HIV-infected woman. *Obstetrics and Gynecology Clinics of North America* 30(4):711–29. December 1, 2003.

Chirgwin, K. and others. Menstrual function in human immunodeficiency virus-infected women without acquired immunodeficiency syndrome. *Journal of Acquired Immune Deficiency Syndromes* 12(5):489–94. August 15, 1996.

Cooper, G. and others. Active and passive smoking and the occurrence of natural menopause. *Epidemiology* 10(6):771–73. November 1999.

Dolan, S. and others. Reduced bone density in HIV-infected women. *Acquired Immune Deficiency Syndromes* 18(3):475–83. February 20, 2004.

Ellerbrock, T. and others. Characteristics of menstruation in women infected with human immunodeficiency virus. *Obstetrics and Gynecology* 87(6):1030–34. June 1996.

Gold, E. and others. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *American Journal of Epidemiology* 153(9):865–74. May 1, 2001.

Grinspoon, S. and others. Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. *Journal of Clinical Endocrinology and Metabolism* 82(5):1332–37. May 1997.

Harlow, S. and others. Effect of HIV infection on menstrual cycle length. *Journal of Acquired Immune Deficiency Syndromes* 24(1):68–75. May 1, 2000.

Loprinzi, C. and others. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *The Lancet* 356(9247):2025–26. December 16, 2000.

Neilsen, H. Hypermenorrhoea associated with ritonavir. *The Lancet* 353(9155):811–12. March 6, 1999.

Rossouw, J. and others. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *Journal of the American Medical Association* 288(3):321–33. July 17, 2002.

Schoenbaum, E. and others. HIV infection, drug use, and onset of natural menopause. *Clinical Infectious Diseases* 41(10):1517–24. November 15, 2005.

Tsiodras, S. and others. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipdystrophy: a 5-year cohort study. *Archives of Internal Medicine* 160:2050–56. July 10, 2000.

Lifestyle Habits That Contribute to Optimal Health

- Eat a balanced diet with plenty of fruits, vegetables, and whole grains
- Get some exercise every day
- Sleep at least eight hours every night
- Avoid smoking and second-hand smoke
- Reduce alcohol intake