Menopause and HIV

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ABSTRACT

Objective: To review the current literature on menopause in HIV-infected women.

Methods: We searched PubMed for articles published in English using the search terms HIV and menopause, HIV and amenorrhea, HIV and menopause symptoms, HIV and vasomotor symptoms, HIV and vaginal dryness, HIV and dyspareunia, HIV and menopause and cardiovascular disease, HIV and menopause and osteoporosis, HIV and menopause and cognition, HIV and menopause and cervical dysplasia, menopause and HIV transmission, and menopause and HIV progression. Major studies on menopause in other populations were also reviewed to provide background data.

Results: While studies on the age of menopause in HIV-infected women give conflicting results, immunosuppression associated with HIV appears to contribute to an earlier onset of menopause. HIV-infected women experience menopausal symptoms, especially vasomotor symptoms, earlier and in greater intensity. In addition, menopause and HIV infection have additive effects on one another, further increasing the disease risks of cardiovascular disease, osteoporosis, and progression of cervical dysplasia. The effects of menopause on HIV infection itself seems limited. While some data suggest an increased risk of acquisition in non-HIV-infected menopausal women, menopause has no effect on the transmission or progression of HIV in menopausal HIV-infected women.

Conclusion: As HIV-infected individuals live longer, practitioners will encounter an increasing number of women entering menopause and living into their postmenopausal years. Future studies on the age of menopause, symptoms of menopause, and the effects of menopause on long term comorbidities such as cognitive decline, cardiovascular disease, and bone density loss are necessary to improve care of this expanding population of women living with HIV.

Since the introduction of highly active antiretroviral therapy (HAART) in 1996, there has been a significant decrease in morbidity and mortality worldwide among individuals living with human immunodeficiency virus (HIV) [1]. It is projected that by the year 2020, half of persons living with HIV infection in the United States will be over the age of 50 years [2]. For HIV-infected women, this longer survival translates into an increased number of women entering into menopause and living well beyond menopause. Enhancing our knowledge about menopause in HIV-infected women is important since the physiologic changes associated with menopause impact short- and long-term quality of life and mortality. Symptoms associated with menopause can be mistaken for symptoms suggestive of infections, cancers, and drug toxicity. Furthermore, changes in cognition, body composition, lipids, glucose metabolism, and bone mass are influential factors determining morbidity and mortality in later years.

Effect of HIV on the Menstrual Cycle

Menstrual irregularities, including amenorrhea and anovulation, are more frequently found in women of low socioeconomic class who experience more social and physical stress like poverty and physical illnesses [3]. In addition, women with low body mass index (BMI) have decreased serum estradiol levels which lead to amenorrhea [3,4]. Furthermore, several studies have demonstrated that methadone, heroin, and morphine use are associated with amenorrhea. Opiate use inhibits the central neural reproductive drive leading to amenorrhea even in the absence of menopause [5–7].

As these demographics, body habitus, and lifestyle characteristics are frequently found among HIV-infected women, it is not surprising that amenorrhea and anovulation are common in this population [8–14]. In fact, studies show that there is an increased prevalence

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of amenorrhea and anovulation among HIV-infected women when compared to non–HIV-infected women [8]. Some studies suggest that women with lower CD4 cell counts and higher viral loads have increased frequency of amenorrhea and irregular menstruation compared to those with higher CD4 cell counts and lower viral loads [9,10]. However, it remains unclear if HIV infection itself, instead of the associated social and medical factors, is responsible for the higher frequency of amenorrhea [11–13]. For example, in a prospective study comparing 802 HIV-infected women with 273 non–HIV-infected women, there was no difference in the prevalence of amenorrhea when controlling for BMI, substance use, and age [13].

The World Health Organization (WHO) currently defines natural menopause as the permanent cessation of menstruation for 12 consecutive months without any obvious pathological or physiologic causes [15]. However, given the increased prevalence of amenorrhea in HIV-infected women, amenorrhea seen with HIV infection can be mistaken for menopause. The Women's Interagency HIV Study (WIHS), a multicenter, observational study of HIV-infected women and non–HIV-infected women of similar socioeconomic status, found that more than half of HIV-infected women with prolonged amenorrhea of at least 1 year had serum follicle-stimulating hormone (FSH) levels in the premenopausal range of less than 25 mIU/mL [16]. Hence, this implies that some of these women may have had prolonged amenorrhea rather than menopause [17]. The traditional definition of menopause may need to be altered in this population.

**Age at Menopause**

Natural menopause, retrospectively determined by the cessation of menstrual cycles for 12 consecutive months, is a reflection of complete, or near complete, ovarian follicular depletion with subsequent low estrogen levels and high FSH concentrations [18]. In the United States, studies have found the mean age of menopause to be between 50 to 52 years old [19,20]. In these studies, however, focused predominantly on menopause in middle class, white women. Early menopause, defined as the permanent cessation of menstruation between 40 to 45 years of age, affects 5% of the women in the United States, while premature menopause or primary ovarian insufficiency, which occurs at younger than 40 years of age, affects 1% of the women [21]. As earlier menopause is associated with increased risks of diabetes [22], cardiovascular disease [23], stroke [24], and osteoporosis [25], identifying the mean age of menopause is important in the management of HIV-infected women. Among women in the United States, early menopause has been observed in women who are African American, nulliparous, have lower BMI, smoke tobacco, and have more stress, less education, and more unemployment [26–29]. Unhealthy lifestyles can also contribute to an earlier age of menopause. Smoking is one of the most consistent and modifiable risk factors associated with an earlier onset of natural menopause, accelerating menopause by up to 2 years [26,30]. Substances present in cigarettes are associated with irreversible damage of ovarian follicles and impaired liver estrogen metabolism [30]. Cocaine use has also been associated with lower estradiol levels, suggesting possible ovary-toxic effects [7,31].

Many of these characteristics and unhealthy lifestyles are prevalent among HIV-infected women. Prevalence of current smoking among HIV-infected persons is found to be approximately 42% [32] in comparison with the 19% seen in the general population in the United States [33]. Specifically, among women participating in WIHS, 56% of the women were found to be current smokers with an additional 16% of the women found to be prior smokers [34]. In addition, African Americans account for the highest proportion of new HIV infections in the United States with an estimated 64% of all new HIV infections in women found to be in African Americans [35]. Furthermore, HIV-infected women are of lower socioeconomic status, with increased prevalence of substance use than that typically found in women enrolled in studies on the age of menopause [36]. Hence, when examining the influence of HIV on the age of menopause, one needs to have a comparator of non–HIV-infected group with similar characteristics. Studies without comparison groups have reported the median age of menopause in HIV-infected women to be between 47 and 50 years old [37–42].

There are only few studies that have focused on the age of menopause in HIV-infected women with a similar comparative non–HIV-infected group. Cetin et al studied the age of menopause in women enrolled in the WIHS [43]. HIV-infected women partaking in the WIHS were primarily African American and of lower socioeconomic status with heterosexual transmission rather than injection drug use as the major HIV risk...
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factor [44]. They found no significant difference in the median age of menopause when HIV-infected women were compared to non–HIV-infected women. Median age of menopause was 47.7 years in HIV-infected women and 48.0 years in non–HIV-infected women [43].

In contrast, in the Ms Study, a prospective cohort comparing 302 HIV-infected with 259 non–HIV-infected women, HIV-infected women were 73% more likely to experience early menopause than non–HIV-infected women [45]. Similar to the WIHS, there was a high prevalence of African Americans but unlike the WIHS the majority of participants had used heroin or cocaine within the past 5 years. The high prevalence of drug use and current or former cigarette use in the Ms Study likely contributed to the relatively early onset of menopause. Furthermore, the WIHS and Ms Study used different definition of menopause. The WIHS defined menopause as 6 consecutive months of amenorrhea with an FSH level greater than 25 mIU/mL while the Ms Study defined menopause as the cessation of menstrual period for 12 consecutive months [43,45]. Given the fact that 52% of the women in the Ms Study had high-risk behaviors associated with amenorrhea and that menopause was defined as 12 months of amenorrhea without corresponding FSH levels, it is possible that the Ms Study included many women with amenorrhea who had not yet reached menopause. On the other hand, although the 6 months’ duration of amenorrhea used in the WIHS to define menopause had the potential to include women who only had amenorrhea without menopause, the use of FSH levels to define menopause most likely eliminated women who only had amenorrhea.

HIV-infected women have several factors associated with early menopause which are similar to that in the general population, including African American race, injection drug use, cigarette smoking, and menarche before age of 11 [37,41]. In addition, multiple studies have shown that a key factor associated with early age of menopause among HIV-infected women is the degree of immunosuppression [37,41,45]. The Ms Study found that women with CD4 cell counts < 200 cells/mm³ had an increased risk of amenorrhea lasting at least 12 months when compared to women with CD4 cell counts ≥ 200 cells/mm³. The median age of menopause was 42.5 years in women with CD4 cell counts < 200 cells/mm³, 46.0 years in women with CD4 cell counts between 200 cells/mm³ and 500 cells/mm³, and 46.5 years in women with CD4 cell counts > 500 cells/mm³ [45]. Similarly, in a cohort of 667 Brazilian HIV-infected women, among whom 160 women were postmenopausal, Calvet et al found 33% of women with CD4 cell counts < 50 cells/mm³ to have premature menopause, compared to 8% of women with CD4 cell counts ≥ 350 cells/mm³ [41]. De Pommerol et al studied 404 HIV-infected women among whom 69 were found to be postmenopausal. They found that women with CD4 cell counts < 200 cells/mm³ were more likely to have premature menopause compared to women with CD4 cell counts ≥ 350 cells/mm³ [37].

Menopause-Associated Symptoms

The perimenopausal period, which begins on average 4 years prior to the final menstrual period, is characterized by hormonal fluctuations leading to irregular menstrual cycles. Symptoms associated with these physiologic changes during the perimenopausal period include vaso-motor symptoms (hot flashes), genitourinary symptoms (vaginal dryness and dyspareunia), anxiety, depression, sleep disturbances, and joint aches [46–53]. Such menopausal symptoms can be distressing, negatively impacting quality of life [54].

It can be difficult to determine which symptoms are caused by the physiologic changes of menopause in HIV-infected women as they have multiple potential reasons for these symptoms, such as antiretroviral therapy, comorbidities, and HIV infection itself [55]. However, several studies clearly show that there are symptoms that occur more commonly in the perimenopausal period and that HIV-infected women experience these symptoms earlier and with greater intensity [38–40,42,56,57]. In a cross-sectional study of 536 women among whom 54% were HIV-infected, Miller et al found that menopausal symptoms were reported significantly more frequently in HIV-infected women compared with non–HIV-infected women [56]. As symptoms can occur in greater intensity and impair quality of life, it is important that providers be able to recognize, understand, and appropriately treat menopausal symptoms in HIV-infected women.

Vasomotor Symptoms

In the United States the most common symptom during perimenopause is hot flashes, which occur in 38% to 80% of women [58,59]. Vasomotor symptoms are most
common in women who smoke, use illicit substances, have a high BMI, are of lower socioeconomic status, and are African American [19]. As expected, prior studies focusing on hot flash prevalence among premenopausal, perimenopausal, and postmenopausal HIV-infected women found that postmenopausal women experience more hot flashes than premenopausal or perimenopausal women [40,42]. In addition, a comparison of HIV-infected and non–HIV-infected women demonstrated a higher prevalence of hot flashes among HIV-infected women [38,56]. Ferreira et al found that 78% of Brazilian HIV-infected women reported vasomotor symptoms compared to 60% of non–HIV-infected women [38]. Similarly, Miller et al reported that 64% of HIV-infected women reported vasomotor symptoms compared to 58% of non–HIV-infected women [56].

Vasomotor symptoms can be severely distressing with hot flashes contributing to increased risk of depression [56,60]. In a cross-sectional analysis of 835 HIV-infected and 335 non–HIV-infected women from the WIHS, persistent vasomotor symptoms predicted elevated depressive symptoms in both HIV-infected and non-HIV-infected women [60]. In a similar cross-sectional analysis of 536 women, among whom 54% were HIV positive and 37% were perimenopausal, psychological symptoms were prevalent in 61% of the women with vasomotor symptoms [56].

Oddly enough, higher CD4 cell counts appear to be associated with increased prevalence of vasomotor symptoms [39,56]. Clark et al demonstrated that menopausal HIV-infected women with CD4 cell counts > 500 cells/mm³ were more likely to report hot flashes [39]. Similarly, Miller et al observed a reduction in the prevalence of menopausal symptoms as CD4 cell counts declined among HIV-infected non-HAART users [56]. The rationale behind this is unclear but some experts postulated that it may be due to the effects of HAART.

Genitourinary Symptoms

With estrogen deficiency, which accompanies the perimenopausal period, vulvovaginal atrophy (VVA) occurs leading to symptoms of vaginal dryness, itching, burning, urgency, and dyspareunia (painful intercourse) [59,61,62]. Unlike vasomotor symptoms, which diminish with time, genitourinary symptoms generally worsen if left untreated [63]. Furthermore, these symptoms are often underreported and underdiagnosed [64,65]. Several studies using telephone and online surveys have found that the prevalence of symptoms of VVA is between 43% and 63% in postmenopausal women [66–69]. Even higher rates were found in the Agata Study in which pelvic exams in 913 Italian women were performed to obtain objective signs of VVA [62]. The prevalence of VVA was 64% 1 year after menopause and 84% 6 years after menopause. Vaginal dryness was found in 100% of participants with VVA or 82% of total study participants. In addition, 77% of women with VVA, or 40% of total study participants, reported dyspareunia.

Genitourinary symptoms are most common among women who are African American, have an increased BMI, are from lower socioeconomic class, use tobacco [19], have prior history of pelvic inflammatory disease, and have anxiety and depression [70,71]. Similarly to hot flashes, many of these predisposing factors are more common in HIV-infected women. Fantry et al found that 49.6% of HIV-infected women had vaginal dryness. Although 56% of postmenopausal women and 36% of perimenopausal women complained of vaginal dryness, in a multivariate analysis only cocaine use, which can decrease estradiol levels [7,31] was associated with a higher frequency of vaginal dryness [40].

Similarly, dyspareunia is also common among HIV-infected women. In a cross-sectional study of 178 non–HIV-infected and 128 HIV-infected women between 40 and 60 years of age, Valadares et al found that the frequency of dyspareunia in HIV-infected women was high at 41.8% [72]. However, this was not significantly higher compared to the prevalence of 34.8% in non–HIV-infected women. HIV infection itself was not associated with the presence of dyspareunia.

Psychiatric Symptoms

Anxiety and depression are also common symptoms in perimenopausal women [73–76]. Studies have shown that depression is diagnosed 2.5 times more frequently among perimenopausal than premenopausal women [76].

In a study by Miller et al that focused on 536 HIV-infected women, among whom 37% were perimenopausal, 89% reported psychological symptoms [56]. Ferreira et al found that HIV-infected perimenopausal women had an increased incidence of psychological symptoms compared to non–HIV-infected women [38]. Whether this increased prevalence of psychological symptoms seen in HIV-infected women can be attributed to menopause is unclear since one third to one half of men and women living with HIV experience symptoms of depression.
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However, in the WIHS, which compared 835 HIV-infected with 335 non-HIV-infected women from all menopausal stages, elevated depressive symptoms were seen in the early perimenopausal period [60]. There was no increased incidence of such symptoms during the premenopausal or postmenopausal period, suggesting the contribution of menopause to depressive symptoms during the perimenopausal period [60]. Persistent menopausal symptoms, especially hot flashes, also predicted elevated depressive symptoms in several studies [56,60] suggesting the importance of appropriately identifying and treating menopausal symptoms. In addition, cognitive decline associated with menopause contributes to depression [78–80].

Other Symptoms
Sleep disturbances are also common among perimenopausal women, with prevalence estimated to be between 38% and 46% [81–84]. Hot flashes, anxiety, and depression appear to be contributing factors [81–84]. In a cross-sectional study of 273 HIV-infected and 264 non-HIV-infected women between 40 and 60 years of age, insomnia was found in 51% of perimenopausal and 53% of postmenopausal HIV-infected women. HIV-infected women had the same prevalence of insomnia compared to non–HIV-infected women [85]. Joint aches are also commonly reported in the perimenopausal period, with prevalence as high as 50% to 60% among perimenopausal women in the United States [52,53]. In HIV-infected women, Miller et al found that 63% of menopausal women reported arthralgia [56].

Treatment
For women experiencing severe hot flashes and vaginal dryness, short-term menopausal hormone therapy (MHT) is indicated to relieve symptoms. MHT should be limited to the shortest period of time at the lowest effective dose as MHT is associated with increased risks of breast cancer, cardiovascular disease, thromboembolism, and increased morbidity [86]. Despite the increased severity of menopausal symptoms experienced among HIV-infected women, the prevalence of the use of MHT in this population is lower compared to non–HIV-infected women [85].

Topical treatment is recommended for women who are experiencing solely vaginal atrophy. First-line treatment is topical nonhormonal therapy such as moisturizers and lubricants [87]. If symptoms are not relieved, then topical vaginal estrogen therapy is recommended [87]. Although topical therapy can result in estrogen absorption into the circulation, it is to a much lesser extent than systemic estrogen therapy [88].

Overall, there is lack of data on the potential interactions between MHT and HAART. Much of the potential interactions are inferred from pharmacokinetic and pharmacodynamics studies between HAART and oral contraceptives. Hormone therapy, protease inhibitors (PIs), colchicine, and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are all metabolized by the CYP3A4 enzyme [89–91]. Current evidence suggests that concomitant use of hormone therapy with NNRTIs and PIs does not significantly alter the pharmacokinetics of HAART or the clinical outcomes of HIV [91]. However, there is evidence that concomitant use of nevirapine and PIs boosted with ritonavir leads to decrease in estrogen levels so higher doses of MHT may have to be used to achieve symptomatic relief [91]. There is no data on the interaction between PIs boosted with colchicine and estrogen [92]. Integrase inhibitors, nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), and the CCR5 antagonist maraviroc have no significant interactions with estrogen containing compounds [89,90,92].

Cardiovascular Risk
Estrogen deficiency resulting from menopause leads to several long-term effects, including cardiovascular disease and osteoporosis. The loss of protective effects of estrogen leads to an increased risk of cardiovascular disease particularly with changes in lipid profiles [93]. Perimenopausal women experience changes in body composition with increased fat mass and waist circumference, as well as dyslipidemia and insulin resistance, all of which are associated with higher risk of cardiovascular disease [94]. HIV infection also incurs a higher risk of cardiovascular disease [95–99]. The inflammatory effects of HIV, HAART, and traditional risk factors including dyslipidemia all contribute to cardiovascular disease but the degree to which each factor contributes to elevated risk is unknown [95,98]. In addition, modifiable risk factors for cardiovascular disease such as decreased fitness and smoking are more commonly seen in HIV-infected women [100]. Even prior to menopause, HIV-infected women experience lipodystrophy syndrome with increase in truncal visceral adiposity and decrease in subcutaneous fat and muscle mass [101,102]. Whether such changes in body composition are exacerbated during the perimenopausal period [77]. However, in the WIHS, which compared 835 HIV-infected with 335 non-HIV-infected women from all menopausal stages, elevated depressive symptoms were seen in the early perimenopausal period [60]. There was no increased incidence of such symptoms during the premenopausal or postmenopausal period, suggesting the contribution of menopause to depressive symptoms during the perimenopausal period [60].
pausal period remain unclear. In the SWEET study, which focused on 702 South African women among whom 21% were HIV-infected, there was lower lean mass but minimal difference in the fat mass of postmenopausal women compared to premenopausal women [103]. As the study was based in South Africa with only 21% HIV-infected, the results of this study should be viewed with caution. While changes in body composition were not observed in postmenopausal women in the SWEET study, increased truncal adiposity seen in premenopausal HIV-infected women is likely to pose an additional risk for cardiovascular disease during the menopause transition.

Several studies have been conducted to demonstrate an increased risk of cardiovascular disease, especially among young HIV-infected men [95–99]. However, no study has focused specifically on the risk of cardiovascular disease in postmenopausal HIV-infected women to date. Despite the lack of studies, it is plausible that the increased risk of cardiovascular disease seen in HIV infection is likely to be compounded with the increased risk seen during menopause. Postmenopausal HIV-infected women may be at significantly higher risk of cardiovascular disease. Appropriate measures such as lipid control, antiplatelet therapy, smoking cessation, and other lifestyle changes should be initiated as in any other population. Further studies are necessary focusing on the effects of menopause on cardiovascular disease risk in HIV-infected women.

Osteoporosis

Menopause, with its associated estrogen deficiency, is the most important risk factor associated with increased bone turnover and bone loss and can worsen HIV associated bone loss [104]. Among HIV-infected individuals, low bone mineral density (BMD) has been described even among premenopausal women and younger men [105–107]. Evidence suggests that the increased BMD associated with HIV stabilizes or even improves after initiation of HAART in the younger population [105–107]. However, once HIV-infected women enter menopause, they have higher rates of bone loss compared to non–HIV-infected women with significantly increased prevalence of osteoporosis compared to non–HIV-infected women [108–112].

Chronic inflammation by HIV stimulates osteoclast differentiation and resorption [113]. In addition, HAART [114–116], vitamin D deficiency [117], low BMI, poor nutrition [118], inactivity, use of tobacco, alcohol, and illicit drugs [119,120], and coinfection with hepatitis B and C [121] all appear to contribute to decreased BMD among HIV-infected men and women [118]. Among HIV-infected postmenopausal women, those taking ritonavir were found to have increased differentiation of osteoclast cells and increased bone loss [122]. Similarly, methadone use in postmenopausal women has been associated with increased BMD decline [123]. African-American, HIV-infected postmenopausal women appear to be at the greatest risk for bone loss [109].

Multiple studies focusing on HIV-infected men have demonstrated an increased prevalence of fractures compared to non–HIV-infected men [124–126]. However, current studies on postmenopausal HIV-infected women demonstrate that fracture incidence is similar between HIV-infected and non–HIV-infected postmenopausal women [108,112]. Nevertheless, given the evidence of low BMD and increased fracture risk seen during menopause among non–HIV-infected women compounded with the additional bone loss seen in HIV-infected individuals, enhanced screening in postmenopausal HIV-infected women is prudent. Although the U.S. Preventive Services Task Force (USPSTF) makes no mention of HIV as a risk factor for enhanced screening [127] and the Infectious Diseases Society of America (IDSA) only recommends screening beginning at the age of 50 years old if there are additional risk factors other than HIV [128], the more recently published Primary care guidelines for the management of persons infected with HIV recommends screening postmenopausal women ≥ 50 years of age with dual-energy X-ray absorptiometry (DEXA) scan [86]. Preventative therapy such as smoking cessation, adequate nutrition, alcohol reduction, weight bearing exercises, and adequate daily vitamin D and calcium should be discussed and recommended in all menopausal HIV-infected women [129]. If the DEXA scan shows osteoporosis, bisphosphonates or other medical therapy should be considered. Although the data are limited, bisphosphonates have been shown to be effective in improving BMD [130–132].

Cognition

The menopause transition is characterized by cognitive changes such as memory loss and difficulty concentrating [133–136]. Both HIV-infected men and women are at higher risk of cognitive impairment [137–139].
Cognitive impairment can range from minor cognitive-motor disorder to HIV-associated dementia due to the immunologic, hormonal, and inflammatory effects of HIV on cognition [137–139]. In addition, those with HIV infection appear to have increased risk factors for cognitive impairment including low education level, psychiatric illnesses, increased social stress, and chemical dependence [137].

Studies focusing on the effects of both HIV infection and menopause on cognition have been limited thus far. In a cross-sectional study of 708 HIV-infected and 278 non–HIV-infected premenopausal, perimenopausal, and postmenopausal women, Rubin et al demonstrated that HIV infection, but not menopausal stage, was associated with worse performance on cognitive measures [140]. While menopausal stage was not associated with cognitive decline, menopausal symptoms like depression, anxiety, and vasomotor symptoms were associated with lower cognitive performance [140].

Though limited, current data appear to indicate that HIV infection, not menopause, contributes to cognitive dysfunction [140]. Symptoms of menopause, however, do appear to exacerbate cognitive decline indicating the importance of recognition and treatment of menopausal symptoms. This is especially important in HIV-infected women since decrease in cognition and depression can interfere with day to day function including medication adherence [141,142].

Cervical Dysplasia

As more HIV-infected women reach older age, the effects of prolonged survival and especially menopause on squamous intraepithelial lesions (SILs) are being investigated to determine if general guidelines of cervical cancer screening should be applied to postmenopausal women.

In a retrospective analysis of Papanicolaou smear results of 245 HIV-infected women, Kim et al noted that menopausal women had a 70% higher risk of progression of SILs than premenopausal women [143]. Similar results were found in a smaller retrospective study of 18 postmenopausal HIV-infected women in which postmenopausal women had a higher prevalence of SILs and persistence of low-grade SILs [144].

Although studies on progression to cervical cancer in postmenopausal HIV-infected women remain limited, current data suggest that postmenopausal HIV-infected women should continue to be monitored and screened similarly to the screening recommendations for premenopausal women. Nevertheless, further studies examining the natural course of cervical lesions are needed to establish the best practice guidelines for screening postmenopausal women.

HIV Acquisition and Transmission

The incidence of new HIV infections in older American women has increased. HIV acquisition from heterosexual contact appears to be higher in older women compared to younger women, with a study suggesting that women over age 45 years had almost a fourfold higher risk of HIV acquisition compared to those under the age of 45 years [145]. While the lack of awareness of HIV risk and less frequent use of protection may contribute to increases in new HIV infection in older women, hormonal changes associated with older age, specifically menopause, may be playing a role. Vaginal wall thinning that occurs during menopause may serve as a risk factor for HIV acquisition.

In a study by Meditz et al, the percentage of endocervical or blood CD4 T cells did not differ between premenopausal and postmenopausal women, but postmenopausal women had greater percentage of CCR5 expression. As CCR5 serves as an entry point of HIV into target cells, this suggests the possibility that postmenopausal women may be at increased risk for HIV acquisition [146]. More recently, Chappell et al also revealed that anti-HIV-1 activity was significantly decreased in postmenopausal compared to premenopausal women, suggesting that there may be an increased susceptibility to HIV-1 infection in postmenopausal women [147]. Hence there appears to be menopause-related immunologic changes of the cervix that may contribute to an increased risk of HIV acquisition in postmenopausal women.

In contrast, although data is limited, postmenopausal HIV-infected women do not appear to be at increased risk of transmitting HIV to non–HIV-infected individuals. Melo et al compared the intensity of HIV shedding between premenopausal and postmenopausal women and found that HIV shedding did not differ between premenopausal or postmenopausal women [148].

HIV Progression

Several studies have focused on the effects of HIV infection on menopause, but minimal data are available on the effects of menopause on the progression of HIV infection. With prior data suggesting that younger persons experience better immunological and virological responses.
to HAART [149–151], it has previously been hypothesized that virologic and immunologic responses to HAART can decline once HIV-infected women reach menopause. However, current evidence suggests that treatment responses to HAART, determined by the median changes in CD4 cell counts and percentages and viral load, in HAART-naïve patients did not differ between premenopausal and postmenopausal women [152]. In addition, there appears to be no significant changes in CD4 cell counts as HIV-infected women progress through menopause [153]. These studies suggest that menopause does not affect the progression of HIV and that HAART-naïve women should respond to HAART regardless of their menopausal status.

**Conclusion**

As HIV-infected individuals live longer, increasing number of women will enter into menopause and live many years beyond menopause. HIV-infected women experience earlier and more severe menopausal symptoms, but knowledge is still lacking on the appropriate management of these symptoms. In addition, current evidence suggests that immunosuppression associated with HIV contributes to an early onset of menopause which leads to increased risks of cardiovascular disease, osteoporosis, and progression of cervical dysplasia. These conditions require proper surveillance and can be prevented with improved understanding of influences of menopause on HIV-infected women. Furthermore, although there is some evidence suggesting that menopause has no effect on HIV transmission and progression, further studies on the immunologic and virologic effects of menopause are necessary.

There still remain significant gaps in our understanding of menopause in HIV-infected women. As practitioners encounter an increasing number of perimenopausal and postmenopausal HIV-infected women, future studies on the effects of HIV on co-morbidities and symptoms of menopause and their appropriate management are necessary to improve care of women living with HIV.

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**References**


123. Sharma A, Cohen HW, Freeman R, et al. Prospective evalu-


