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# Hormones, Menopause, and HIV Infection

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With the growing use of highly active antiretroviral therapy for HIV infection, overall survival for AIDS patients has vastly improved. As our population of HIV-infected women ages, the number of these individuals who will be approaching menopause is expected to increase. Little is known about the potential effects of systemic or exogenous sex steroid hormones and menopause on HIV disease, or the potential effects of HIV disease on menopause and hormones. More research is needed to adequately address these issues to care for our increasing population of HIV-infected menopausal women in the future.

## Introduction

The incidence and prevalence of Human Immunodeficiency Virus (HIV) infection in adults aged 50 years and older has steadily increased in the United States, especially among minority populations. The Centers for Disease Control and Prevention (CDC) reported that between 1992 and 1999, a steadily increasing proportion of those living with AIDS were women.<sup>1</sup> In 1992, 14% of adults and adolescents living with AIDS were women, and by 1999 this proportion had grown to 20%.

In women over age 50, the cumulative cases of AIDS nearly tripled between 1993 and 1997. Despite this increase,<sup>2,6</sup> there has been very little focus on research to address the particular issues surrounding women with HIV in this age group. These issues range from the possible increase in HIV acquisition through the thinned vaginal epithelium as a result of aging to prevention and hormonal issues, including those involving systemic and exogenous hormones.<sup>7</sup> This review will discuss hormonal issues in HIV-infected menopausal women.

## Menopause and HIV

Antiretroviral therapies have greatly improved overall survival in HIV disease. As our treated population ages, the proportion of women with HIV who approach menopause is expected to increase. The total number of AIDS cases in women over age 45 in the United States as reported to the CDC through June 1999 was 19,309, or 16% of all AIDS cases in women.<sup>8</sup> Currently, minimal information exists on HIV infection and menopause. Several cohort studies have demonstrated that older persons have a faster progression to AIDS than younger people<sup>9-14</sup> and the duration of survival may be shorter for older patients.<sup>15-18</sup> However, treatment of HIV-infected persons age 50 or older is associated with a decreased death rate (HR=0.28, 95% CI, 0.15-0.52).<sup>19</sup>

Data on gonadal function in HIV-

infected women also is limited. Anovulation in women of reproductive age, as defined by progesterone and follicle-stimulating hormone (FSH) levels, appeared to occur in 16 of 33 (48%) women tested, with two patients demonstrating elevated menopausal FSH levels at age 35 and 42.<sup>20</sup> Although the generalizability of these results on such a small sample size is questionable, another study on women with normal menstruation also found an increased incidence of anovulation.<sup>21</sup> Whether these data have any implications for age of menopause onset in HIV-infected women is not known. In a retrospective study of 82 HIV-infected women who were 40 years of age or older, a trend was noted toward a decreased risk of death in women who were on menopausal hormone therapy.<sup>22</sup> The survey by Clark noted that although postmenopausal hormone therapy was rarely used, several menopausal symptoms were relatively common among HIV-infected women aged 40 years or older.<sup>23</sup> In all, 79 of 101 women surveyed had hot flashes; and women with higher CD4 counts were more likely to experience hot flashes ( $p < 0.03$ ).

## Metabolic Complications of HIV and Menopause

Menopausal hormone therapy apparently has seldom been used in eligible

HIV-infected women. A survey of HIV-infected women conducted in 2000 revealed that of those patients who were menopausal, only 11% were on hormone therapy.<sup>23</sup> At the same time, a 1998 North American Menopause Society (NAMS) survey of menopausal women revealed that 70% of women who had undergone a hysterectomy were on hormone therapy, compared with 41% of women who had not undergone a hysterectomy.<sup>24</sup> HIV infection and antiretroviral therapy have been associated with multiple metabolic complications of importance to menopausal women,<sup>25,26</sup> and HIV infection or antiretroviral treatment alone have been associated with what appears to be an accelerated rate of osteopenia/osteoporosis in men.<sup>25,26</sup> This effect also may occur in women with HIV,<sup>27</sup> in addition to the well known risk of bone loss associated with menopause. These combined effects in menopausal HIV-infected women underscore the need for close surveillance.

Protease inhibitors are associated with a three-fold increase in the development of glucose intolerance in women.<sup>28</sup> HIV-associated lipodystrophy occurs with wasting of the extremities and central fat distribution—including breast enlargement—and its etiology is so far unclear.<sup>25,26</sup> Decreased testosterone levels are associated with visceral

**Table 1.**  
**Ethinyl Estradiol AUC\* with Concomitant Selected Antiretrovirals**

Antiretrovirals	% Change in Ethinyl Estradiol AUC with Concomitant ARV†
Efavirenz	↑ 37%
Nevirapine	↓ 19%
Ritonavir	↓ 41%
Nelfinavir	↓ 47%
Lopinavir/ritonavir	↓ 42%

\*Area under the time-concentration curve

†Antiretroviral

adiposity in men, and testosterone therapy has been associated with decreases in visceral adiposity.<sup>25,26</sup> Various antiretrovirals also are associated with cardiovascular risk factors such as elevated cholesterol and triglycerides, making the cardiovascular risk assessment of HIV patients difficult.<sup>25,26</sup> AIDS-related dementia complex appears to develop in the later stages of HIV disease in a small, but significant, number of patients. The mechanism of this neurodysfunction is not well defined.<sup>29</sup> All of these metabolic effects have far-reaching implications for the growing population of older women with HIV, in terms of the potential effects of systemic or exogenous hormone status and aging itself.

Menopause and age also are noted to have various effects on the immune system. Menopausal hormone therapy has been associated with significant increases in B-cells, higher mitogen-induced T-cell proliferation, and higher levels of induced TNF- $\alpha$ . Thus, the hormone changes associated with menopause or hormone therapy may have implications for HIV disease and its metabolic complications that are not defined currently.

### Cytochrome Activity and Antiretrovirals

CYP3A4 is the most abundant cytochrome P450 in the liver and plays a role in the metabolism of more than half of all clinically used drugs. The treatment of HIV with highly active combination antiretroviral regimens has resulted in a major improvement in overall survival and immune function and a decrease in opportunistic infections. However, these potent antiretrovirals are also associated with various metabolic complications and drug-drug interactions, including the possibility of interactions with steroidogenic hormones. All protease inhibitors are metabolized by, and inhibit, CYP3A4, whereas nevirapine (Viramune) and efavirenz (Sustiva) are inducers of CYP3A4.

### Cytochrome Activity and Menopause

Steroidogenic enzymes, which produce estrogens and progestins, are members of the cytochrome P450 group of oxidases, which also metabolize many other substances. A variety of agents may affect steroid-hormone synthesis and metabolism; and steroid hormones, in turn, may affect other substances through the cytochrome system.<sup>30</sup> Conflicting information exists on the effects of menopause on the P450 enzymes. Several studies support a change in P450 activity (specifically CYP3A activity) with onset of menopause.<sup>31-33</sup>

Alfentanil (Alfenta) is thought to be largely oxidized through CYP3A4. In a re-analysis of data from Lemmens et al, Rubio and Cox found that there appeared to be a decrease in alfentanil clearance in postmenopausal women compared with premenopausal women, presumably secondary to changes in CYP3A4 activity.<sup>31,34,35</sup> According to Harris et al, the unbound clearance of prednisolone was significantly lower in postmenopausal versus premenopausal women, possibly as a result of CYP3A4 changes in menopause and independent of aging.<sup>32</sup> Midazolam (Versed) currently is used as an *in vivo* probe of hepatic and intestinal CYP3A activity. In one study, tirilazad and midazolam clearance was found to be decreased in postmenopausal women when compared with premenopausal women, suggesting involvement of the CYP3A4 enzyme.<sup>33</sup> In contrast, Gorski et al did not find a difference in midazolam clearance, suggesting no differences in CYP3A4 for postmenopausal or premenopausal women.<sup>36</sup>

### Effect of Hormones on Antiretrovirals

Although few studies exist on drug interactions with postmenopausal hormone therapy, steroid hormones may affect several drugs metabolized through the P450 system, which may predict an impact on antiretroviral clearance and metabolism. Compared with controls, a significant decrease in

the unbound clearance and an increase in the total and unbound half-life of prednisolone was noted by Gustavson et al with postmenopausal conjugated estrogen replacement.<sup>37</sup>

In contrast, Harris et al found no significant change in prednisolone or erythromycin pharmacokinetics with postmenopausal hormone therapy, although he did find a difference between postmenopausal and premenopausal women in prednisolone pharmacokinetics.<sup>32</sup> Although tirilazad clearance was lower in postmenopausal women, this decrease did not appear to be reversed with conjugated estrogens and progesterone.<sup>33</sup> There was no significant difference in midazolam clearance with conjugated estrogens and progesterone.<sup>36</sup>

A study on caffeine metabolism before and after postmenopausal estradiol indicated that estradiol inhibits CYP1A2-mediated caffeine metabolism.<sup>38</sup> Postmenopausal estradiol and levonorgestrel have proven to significantly increase tacrine levels, possibly through the hormone therapy's effect on CYP1A2 activity.<sup>39</sup> Tacrine (Cognex) is used to treat Alzheimer's disease, and estrogen has been reported to clinically enhance tacrine response in women with this condition.<sup>40,41</sup> In a preliminary study in which postmenopausal women were given either intramuscular or oral progestins, women who received intramuscular progestin showed a 23% increase in CYP3A4 activity compared with those given the agent orally.<sup>42</sup> Oral contraceptives, which contain higher levels of estrogen and progestin than menopausal hormone therapy, have been found to affect clearance kinetics of various drugs through P450 changes, including decreased clearance of theophylline, caffeine, imipramine (Tofranil), chlorthalidone, and diazepam (Valium).<sup>43-47</sup>

The antiretroviral amprenavir (Agenerase), when taken with oral contraceptives, has been noted to result in a 22% decrease in amprenavir AUC (area

under the time-concentration curve) and the Food and Drug Administration (FDA) recently advised that amprenavir should not be taken with hormonal contraceptives.<sup>48</sup> However, beyond oral contraceptives and amprenavir, data on the potential effect of much lower dose estrogen and progestin therapy on anti-retroviral levels is conflicting; and there is currently no strong evidence to support this effect.

### Effect of Antiretrovirals on Hormones

In contrast, there is some implied evidence from oral contraceptive studies that antiretrovirals may have a significant effect on systemic endogenous and exogenously supplied estrogen levels. Protease inhibitors and other antiretrovirals may interact with other medications through inhibition or induction of P450 enzymes (particularly CYP3A enzymes) or through effects on glucuronidation.

A few antiretrovirals have been examined with concomitant oral contraceptives (Table 1). Efavirenz is associated with an increase in coadministered ethinyl estradiol levels, thought to result from interference with P450 enzymes.<sup>49</sup> No change in efavirenz levels was noted after a single dose of ethinyl estradiol. Nevirapine, given with oral contraceptives, results in a decrease in the AUC of single-dose ethinyl estradiol. Ritonavir (Norvir) is associated with a significant decrease in oral contraceptive estradiol AUC; and nelfinavir (Viracept) also is linked to a decrease in oral contraceptive estradiol AUC.<sup>50</sup> Lopinavir/ritonavir (Kaletra), given with oral contraceptives, has been associated with a decrease in oral contraceptive estradiol levels.<sup>51</sup> These interactions between antiretrovirals and oral contraceptive ethinyl estradiol may vary between drugs in the same class. Due to the unknown effects on contraceptive efficacy of altered hormonal levels with selected antiretrovirals, oral contraceptives should be used cautiously in these patients.

Information on nucleoside reverse

transcriptase inhibitor (NRTI) interactions with oral contraceptives is limited. However, interactions would not be expected to take place between most members of these two classes of drugs due to divergent metabolic pathways.<sup>52,53</sup> Didanosine (ddI); lamivudine (3TC), excreted unchanged; stavudine (d4T); and zalcitabine (ddC) undergo renal excretion of approximately 50% to 85%. Abacavir (Ziagen) is metabolized by a unique pathway involving alcohol dehydrogenase and glucuronyl transferase, and the metabolites are excreted renally. Zidovudine (ZDV, Retrovir) undergoes glucuronidation to the metabolite GZDV that then is eliminated renally.<sup>54</sup> Oral contraceptives have been shown previously to enhance the glucuronidation of several compounds. Preliminary results have demonstrated no significant difference in glucuronidation of ZDV in patients on oral contraceptives compared with controls.<sup>55</sup>

Oral contraceptive pharmacokinetic studies support the potential varied hormonal effects which may occur with antiretroviral use in menopause and with menopausal hormone therapy.

### Menopause, HIV, and the Lower Genital Tract

HIV has been detected by polymerase chain reaction (PCR) and culture in the female genital tract. The virus has been detected in cell-free secretions and lavage specimens, lymphocytes, macrophages, and the vaginal subepithelial stroma. Various cofactors may affect the presence of HIV in the female genital tract. Clemetson et al found an increase in cervical, but not vaginal, HIV shedding with oral contraceptives, inflammation, and pregnancy.<sup>56</sup> Several authors have demonstrated a positive correlation between plasma viral load and cervicovaginal HIV.<sup>57-59</sup> Menopause, which is associated with thinning of the vaginal epithelium and an alteration in vaginal flora leading to a more alkaline vaginal pH, may be associated with an increased risk of HIV transmission.<sup>60,61</sup>

Estrogen and progesterone also are thought to have a modulating effect on mucosal immunoglobulin A (IgA). In uninfected macaques inoculated intravaginally with simian immunodeficiency virus (SIV), none of six estrogen-treated macaques became infected.<sup>62</sup> Postmenopausal hormone therapy, therefore, may have an effect on the presence of HIV in the genital tract and on HIV viral dynamics in the genital tract; although the direction of this effect is unpredictable according to current data.

### Conclusions

HIV infection, and its treatment with highly active antiretrovirals, has multiple metabolic and infectious complications affecting all organ systems that will significantly affect our menopausal population. The treatment of HIV infection itself also may affect both systemic and exogenous hormone status in menopausal women. However, more research is required to identify and define these potential interactions before gynecologists and other physicians can adequately address menopausal issues in our HIV-infected patients. ■

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