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A pioneer in menopause research, Dr. Utian founded the world's first menopause clinic in Cape Town, South Africa, in 1966 and established the Cleveland Menopause Clinic in 1983.

Recipient of many research grants and awards, he is the author of more than 150 scientific publications and five books. He is the Honorary Past-President of the International Menopause Society and Honorary Founding President and Executive Director of The North American Menopause Society. He is also Chairman of the Council of Affiliated Menopause Societies (CAMS) of the International Menopause Society.

## Menopause and Systemic Hormones in the HIV-Infected Woman

Areas of the menopause transition remain for which there is virtually no information. This fact was clearly illuminated at a National Institutes of Health (NIH) meeting entitled "Fertility Regulation and Systemic Hormones in HIV-Infected and At-Risk Women," held January 13-14, 2003.

HIV-AIDS in the United States, unlike in developing countries, has been transformed from a lethal to a chronic disease due to the development of a range of anti-retroviral therapies (ARTs). As a direct result, there is now a cohort of HIV-infected women across this country moving through the menopause transition. Consequently, individual practitioners and menopause clinicians are likely to see increasing numbers of HIV-infected women asking the same questions regarding menopause and potential therapies that the general population ask. An additional confounding factor, of course, will be the effect of the infection itself and the various ARTs on the menopause transition as well as on those pharmacotherapies, specifically hormones, utilized beyond menopause.

Based on virtually no studies, what are the issues and what can we at least anticipate from a limited amount of extrapolated information? The first key issue is the impact of hormonal changes on HIV transmission across the genital epithelium, particularly the vagina and cervix. For example, some epidemiologic studies suggest an association between use of depo-medroxyprogesterone acetate and the risk of HIV. It also is possible that progesterone vaginal suppositories causing vaginal thinning may increase HIV transmission. There is also some evidence that use of hormonal contraception increases the acquisition of HIV-1. The mucosal immune system is under hormonal control; and a greater understanding is essential to the whole issue of preventing local infection in the genital mucosa and the pathogenesis of sexually transmitted diseases.

Part of the risk and development of HIV infection may also be through a mechanism by which combined oral contraceptives (COCs) increase the expression of HIV-1 chemokine co-receptors, and the number of T-cells expressing these co-receptors also increase. Obviously, the question of any equivalent relationship between postmenopausal hormone usage and risk of HIV transmission remains uninvestigated. Furthermore, there is also the possibility that hormonal contraception use may be associated with a more complex viral population, greater HIV-1 plasma viral load, and faster HIV-1 disease progression. As the HIV-infected woman progresses through the menopause transition, the possibility also exists that reduced sex steroid levels may accelerate reduction in CD4 lymphocyte counts.

Yet another question urgently demanding answers concerns drug-drug interactions. For example, when COCs are administered concomitantly with protease inhibitors, induction of specific enzymes—such as CYP3A4 isoenzyme—results in changes in contraceptive steroid plasma concentrations. Thus, low-dose COCs may become less effective in preventing pregnancy. Clearly, we need to know what happens with systemic hormone use in the postmenopausal woman. Changes in hormone levels resulting from drug-drug interactions could have a huge impact on both potential risks and benefits of postmenopausal hormone usage.

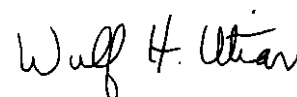
Of course, quality of life is of no less a concern to the HIV-infected woman than to any other woman. Issues of menopause-symptom relief, weight loss, debility, muscle weakness, bone loss, and so-forth are of paramount importance. In this instance, both androgens and estrogens may have significant value for these patients. The risk-to-benefit relationship of these drugs may be different in an HIV-infected population.

The issues and questions, therefore, are multiple. What is the role of hormonal menopausal therapy in HIV-infected and at-risk women? Vaginal atrophy after menopause may predispose to HIV transmission, so what is the role of local or systemic estrogen, particularly in high-risk women? An answer to this second question could potentially impact other viral sexually transmitted diseases such as herpes simplex and human papillomavirus (HPV). Do HIV infection or the modern ARTs change the natural history of the menopause transition? What are the effects of the HIV infection and ARTs on co-morbidities such as cardiovascular disease, breast cancer, and osteoporosis? What is the impact of sex steroids on HIV-associated dementia? Do alternate therapies beyond menopause—such as black cohosh, soy products, selective estrogen receptor modulators (SERMS), bisphosphonates, and so-forth—alter HIV disease development? The questions are endless!

We need to take immediate action to maximize what we learn from the first cohort of HIV-infected women passing through the menopause transition. For example, what we are learning from the NIH-financed Study of Women Across the Nation (SWAN) could be translated easily into a “mini-SWAN,” in which cohorts of HIV-infected women are followed in multiple centers. Towards this end, NAMS will offer a workshop at its annual meeting in Miami (September 17-20, 2003) on “The Status and Direction of Menopause Cohort Studies.” We hope those clinicians and scientists with an interest in HIV infection will use this session as a

networking opportunity to initiate appropriate research in the area of menopause transition.

The medical practitioner needs to be prepared to provide appropriate menopause-related care to the HIV-infected and at-risk population. The scientific community needs to accelerate its research endeavors to help provide practitioners the answers so necessary to handle an increasing number of women and an escalating numbers of questions. Here exists a unique opportunity for new young investigators to get in on the ground floor of a crucial area of research for which funding really is available. NIH is to be commended for getting the ball rolling, but we all need to face the challenge as a matter of urgency.



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