REVIEW

# Low genitourinary tract risks in women living with the human immunodeficiency virus

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**ABSTRACT**

This review analyzes the clinical associations between specific low genitourinary tract clinical circumstances in peri- and postmenopausal women living with human immunodeficiency virus (WLHIV). Modern antiretroviral therapy (ART) improves survival and reduces opportunistic infections and HIV transmission. Despite appropriate ART, WLHIV may display menstrual dysfunction, risk of early menopause, vaginal microbiome alterations, vaginal dryness, dyspareunia, vasomotor symptoms, and low sexual function as compared to women without the infection. They have increased risks of intraepithelial and invasive cervical, vaginal, and vulvar cancers. The reduced immunity capacity may also increase the risk of urinary tract infections, side effects or toxicity of ARTs, and opportunistic infections, Menstrual dysfunction and early menopause may contribute to the early onset of vascular atherosclerosis and plaque formation, and increased osteoporosis risks requiring specific early interventions. On the other hand, the association between being postmenopausal and having a low sexual function is significant and related to low adherence to ART. WLHIV deserve a specific approach to manage different low genitourinary risks and complications related to hormone dysfunction and early menopause.

**KEYWORDS** Acquired immunodeficiency syndrome; AIDS; antiretroviral therapy; cancer; genitourinary syndrome; HIV; human immunodeficiency virus; low urogenital tract; menopause

## Introduction

More than 20 million girls and women live with the human immunodeficiency virus (HIV) and most contract the infection through heterosexual rapport [1]. The increasing number of infected women is partially explained by the fact that they live longer due to appropriate antiretroviral treatment (ART) and are aging with the infection [2,3]. This treatment is associated with a significant decrease in opportunistic infections, severe HIV-related and unrelated diseases, a better quality of life, and an increased life expectancy. It also lowers virus-related malignancies, such as non-Hodgkin lymphoma and Kaposi sarcoma.

Mid-aged and postmenopausal women living with HIV (WLHIV) manifest endocrine alterations, have more severe menopause-related clinical complaints, and increased risks of cardiovascular disease, bone mineral alterations and osteoporosis, and cognitions. Social background, lifestyle, and demographic factors conditionate the quality of life and general health status. A relevant issue, sometimes overlooked, is the risk of HIV contagious among peri- or postmenopausal women. Advanced HIV infection may be diagnosed in patients aged more than 50 years. A significant proportion of women may be infected during those years or had no previous diagnosis [4,5]. In addition, this population may be diagnosed in the advanced stages of the HIV disease.

The obstacle to HIV cure is the difficulty to reduce, or silence the viral reservoir, with the particular characteristic that HIV may persist or not depending on steroid hormones, adherence to ART, individual lifestyle, and addictive drug consumption [6,7]. Given the increasing number of WLHIV, we review their individualized climacteric clinical needs related to the lower genitourinary tract. The anatomic and functional deconstruction of the low genitourinary tract allows the identification of specific risks in peri- and postmenopausal women [8].

## The female genitourinary tract in WLHIV

A third of WLHIV infections have the virus identifiable in the vaginal fluid [9], and during early viral exposure, the genital tract inflammation predicts the viral load [10]. The virus may remain in the infected cells as latent proviral desoxyribonucleic acid, and is not affected by ART and can reactivate to release new virions. The endocervix cells can reactivate HIV from infected cells under the presence of some microbes, like herpes simplex virus 2 [11]. The cervicovaginal epithelium produces compounds that have anti-HIV effects, including defensins, leukocyte protease inhibitors, lysozyme, lactoferrin, and elafin [12,13].Women with menstrual cycles not receiving hormone treatments can partially neutralize the viral replication and decrease the plasma viral load [14]. On the contrary, cervical mucosa inflammation, with increased levels of pro-inflammatory cytokines, is associated with a high risk of worsening HIV infection [15,16].

The vaginal microbiota, particularly if dominated by *Lactobacillus spp*., may be beneficial to the female genital tract by producing hydrogen peroxide and lactic acid that have antimicrobial properties [17]. The most protective community state types (CST) are likely I, II, and V, dominated by *L. crispatus*, *L. gasseri*, and *L. jensenii*, respectively. On the opposite, the higher HIV risk is associated with CST IV (the diversity group, encompassing bacterial vaginosis and aerobic vaginitis/desquamative inflammatory vaginitis). The role of CST III (*L. iners*) is more controversial but seems to be a less favorable profile [18-20]. The protective effect against HIV is partially mediated by extracellular vesicles released by the symbiotic bacteria [21]. However, their abundance declines during menopause, with a more or less pronounced decrease in lactobacilli and an

increase in diversity [22,23]. The lactobacillus-depleted genital microbiome may increase the risk of HIV infection in women [24]. Menopause hormone treatment can promote the presence of lactobacilli [22]. Compliance with ART reduces the genital shedding risk of HIV [25].

HIV-positive postmenopausal women have reduced bactericidal activity related to microbiome changes as compared to premenopausal women. The vagina flora in the former is more often dominated by *Enterobacteriaceae,* with the dominance at the species level of *Escherichia coli* [26,27]. The obstacles to infection neutralization or elimination are the creation of viral reservoirs, low compliance with ART, unhealthy lifestyle, inconsistent condom use, smoking, and use of addictive drugs [28].

## Menstrual dysfunction and menopause in WLHIV

### *Menstrual dysfunction*

Menstrual disorders are highly prevalent among WLHIV, and the main challenge is to establish if the symptoms are due to the infection, endocrine dysfunctions, menopause, addictive drug consumption, or interruption of ARV. Other factors involved in amenorrhea risk include chronic stress, co-morbidity, consumption of addictive drugs, or ordinary clinical conditions that affect all women, including hyperprolactinemia, polycystic ovary syndrome, or premature ovarian failure [29-31].

In a prospective comparison of 3,634 women living with and without HIV, adjusted for demographic factors, body mass index (BMI), and use of addictive drugs the former group had an increased odds ratio (OR) of having shorter (< 18 days) or longer menstrual cycles; a non-significant OR for very long cycles (> 90 days) was also noted [29]. In WLHIV in Spain, aged 36-42 years, menstrual disorders were observed in 32% and were associated with worse adherence to ART, having detectable viral load, and sexual dysfunction [32]. A Canadian cohort of WLHIV being on ART reported a high prevalence of abnormal menstruation patterns among women aged 16-45 years being under ART [33]. WLHIV in England and on ART for a median duration of six years and CD4 (+) cell count higher than 400 reported less menstrual symptoms, including shorter menstrual duration, and more premenstrual tension and dysmenorrhea when compared to women without HIV [34]. This study also reported that premenstrual tension was more likely among WLHIV than those without the infection, and these effects were related to some ART components.

The Stages of Reproductive Aging Workshop (STRAW + 10) criteria has been used to characterize menstrual patterns in WLHIV aged 30 years or older. The follicle-stimulating hormone (FSH) levels were increased, while those of estradiol were reduced from stage -2 to stage +2 [35]. Furthermore, women with unsuppressed viral loads had higher sex hormone-binding globulin levels than women without HIV infection [36]. Therefore, the available data suggest that WLHIV have subtle endocrine alterations in their ovarian cycles. The use of hormonal contraception is a reasonable treatment for WLHIV and irregular menstrual cycles, the desire to maintain stable hormone levels and efficacious family planning method, or reduce the risk of heavy bleeding [37]. However, hormonal contraceptives may alter the genital microenvironment and favour HIV replication and further propagate the infection [38-40].

### *Menopause transition*

There are different, even contradictory, results concerning the age at menopause, the severity of clinical symptoms, body weight, and quality of life in WLHIV by ethnic groups

and socioeconomic conditions. Despite the wide age range variation for natural menopause by country, lifestyle, body weight, and quality of life, the available data suggest that WLHIV experience menopause earlier and with greater symptomatology when compared with HIV-negative women [41-43]. A meta-analysis has demonstrated an association between HIV infection and amenorrhea (>3 months), probably related to low body mass index (BMI) and independent of the consumption of addictive substances and socioeconomic level [44]. However, the authors did not report a comparison of age at menopause in women with and without HIV infection [44].

The HIV Women's Sexual and Reproductive Health Cohort Study reported that 29.7% of WLHIV had menopause before 45 years, being that in 16.6% it was early menopause, and 13.1 % it was premature menopause [45]. These women were born in Canada, were white ethnicity, had less than high-school studies, were smokers, and used addictive drugs. However, a comparison with women without HIV was not available. Among WLHIV in Switzerland, the median age of menopause was two years earlier than that of women without HIV infection [46]. However, age at menopause in WLHIV is influenced by ART compliance, therapeutic HIV suppression, low BMI, smoking habit, additive drug use, and low socioeconomic status [47]

Anti-mullerian hormone (AMH) has been proposed as a predictor of the menopausal transition in HIV-infected women. The decline in AMH is variable in premenopausal women with HIV from woman to woman, and the prediction of menopause has different trajectories according to BMI. Menopause is likely to ensue when AMH levels drop to less than 0.05 ng/mL [48]. However, other factors may contribute to an earlier age of menopause, including smoking, hepatitis C, higher HIV ribonucleic acid levels, and clinical severity of the infection [49].

In young and perimenopausal WLHIV, hormone contraceptive treatment (intrauterine levonorgestrel device, oral, transdermal, and vaginal ring hormone products) may reduce menstrual disorders and the risk of an undesired pregnancy. Since women with HIV display more severe symptoms and risks than expected as compared to women without the viral infection [50-52]. Conventional menopausal hormone therapy management should be considered in peri- and postmenopausal WLHIV. They may obtain benefits, including reduction of vasomotor symptoms and mucose and skin aging, prevention of low genitourinary tract aging, and muscle-skeletal protection.

ARTs are associated with different side effects on muscle function and bone metabolism. Muscle training, progressive resistance, and nutritional supplements are convenient for HIV patients [53,54]. The osteoporosis risk is increased in WLHIV due to hormone alterations and early menopause, HIV infection, and ART. The osteoporosis risk is increased in WLHIV due to steroid hormone alterations and early menopause, HIV infection, and ART. WLHIV have 5-9% lower bone mineral density (BMD) at the lumbar spine, femoral neck, and radius [55]. Therefore, in vulnerable women, the selection of ART should consider those with fewer bone side effects [56].

Subjects living with HIV have a higher risk for vascular plaque formation than those without HIV infection [57]. Postmenopausal WLHIV may reduce the subclinical atherosclerosis risk with menopause hormone therapy as demonstrated by a lower prevalence of vascular plaque and less progression of carotid intima thickness [58].

## Vaginal dryness and low sexual function

### *Vaginal dryness and dyspareunia*

The most frequent genital expression of menopause in the general population is vaginal dryness and dyspareunia, associated with vaginal irritation, and lack of enjoyment of sex [59]. Dyspareunia is highly prevalent among both HIV-positive and HIV-negative, and even more common in postmenopausal women [60]. In WLHIV, those symptoms may be due to or exacerbated by addictive drug use (crack, cocaine, and/or heroin) rather than menopause [61]. Among Thai postmenopausal WLHIV, there is a significant reduction in sexual acts (related to more night sweats, reduced sexual desire, and avoidance of intimacy) compared to non-postmenopausal women. In addition, other general menopause-related symptoms are also severe [62]. The general recommendations for management of vulvovaginal atrophy are applicable in WLHIV [63,64].

### *Low sexual function*

WLHIV report significantly lower scores in sexual interest, sexual activity, satisfaction, and orgasm [65]. Body image and self-esteem are major determinants of female sexual dysfunction among WLHIV [66]. Older women living with HIV are more likely to report sexual difficulties, including low libido and vaginal dryness, than those without HIV. Some of these women, with a low perception of the risk of HIV transmission, may abandon safe sex practices and condom use [67].

Sexual dysfunction is associated with low adherence to ART in people living with HIV infection. In a study performed in Italy, 21% of the patients not adherent to ART reported some degree of sexual dysfunction in the previous month. Six percent was considered severe and associated with worse viral immunologic outcomes, more symptomatic, and abnormal fat accumulation [68]. Toorabally *et al*. [69] studied the sexual function of WLHIV in England aged 45-60 years, concluding that postmenopausal women were more likely to have at least one sexual problem with a duration of at least three months and to have a lower sexual function (55.6% *vs*. 40.4%, respectively) as compared to women HIV-negative.

The Female Sexual Function Index (FSFI) has been used to evaluate WLHIV. Postmenopausal women living in the United States, with depressive symptoms and a CD4 cell count lower than 200 reported lower sexual function compared to those with a higher count [70]. Another study reported that Indian women with CD4 counts between 200 and 499 had better general sexual function than those with lower values [71]. Among Nigerian women living with HIV and to which the FSFI was applied, 89.2% reported low sexual function, the arousal subdomain with the lowest score, and alcohol use was associated with sexual dysfunction [72].

WLHIV in Peru, aged 40-59 years, reported menopausal symptoms and sexual dysfunction related to non-adherence to ART [73]. Postmenopausal women had lower FSFI scores than those who were premenopausal. The association between being postmenopausal and having low sexual function was significant both in the regression models and related to low adherence to ART (70.6%) to ART. The frequency of low sexual function was 53.6% in premenopausal and 75.0% in postmenopausal women.

## Genital cancer risk among women living with HIV

### *Cervical cancer*

Among WLHIV in Spain, there was evidence that the cervix cancer risk was higher as

compared to women without HIV [74]. The Italian VALHIDATE Study reported that women living with HIV have a 2-3 times higher risk of having an abnormal pap smear than in immunocompetent HIV-women [75]. Gupta *et al*. [76] evaluated conventional cervical smears and high-risk HPV testing, in both WLHIV and without the infection, with similar sociodemographic characteristics, and reported a higher prevalence of abnormal cervical smears in the affected women (14.1% *vs*. 3.1%, respectively). The Caicedo-Martínez et al. [77] meta-analysis of WLHIV in Latin America and the Caribbean reported a 51.0% prevalence of high-risk human papillomavirus (HR-HPV) infection in WLHIV. In addition, there was no association between ART and HR-HPV prevalence. HPV infection was also more frequent among WLHIV (28.9% *vs.* 9.3%, respectively).

Another issue is the evolution and regression of cervical pap testing in WLHIV under ART. A meta-analysis by Kelly *et al*. [78] demonstrated that women under ART had a lower prevalence of high-risk HPV compared to those not using ART. This effect was also observed for cervical high-grade squamous intraepithelial lesions (HSIL) prevalence and rate of progression|. An opposite effect was reported for the likelihood of squamous intraepithelial regression. Furthermore, ART was associated with a reduction of invasive cancer risk. These results support the need for ART adherence, as it improves genital mucosa protection and immune reconstitution.

Stewart *et al*. [79] reported a rate of 17% of HSIL in WLHIV, aged more than 65 years, and without a history of previous abnormal cytology. Those cases were associated with a CD4 (+) count of <200, a high incidence of cytological abnormalities, and increased cancer risk associated with HR-HPV, especially HPV16 [80-83]. These findings reinforce the idea that WLHIV deserves to be screened for cervical cancer beyond 65 years..

***Vulvar and vaginal cancer***

Vulvar cancer can be derived from two pathways: one associated with vulvar dermatosis (lichen sclerosus or lichen planus) and one associated with HPV infection. According to the International Society for the Study of Vulvovaginal Diseases the associated precursor lesions are differentiated vulvar intraepithelial neoplasia and vulvar HSIL, respectively [84, 85]. Most vulvar cancers are associated with vulvar dermatosis, while most cases of VIN are associated with HPV infection. More recently, the World Health Organization [86] proposed that the terminology “HPV- independent vulvar intraepithelial neoplasia (VIN)” and “HPV-associated VIN” should be adopted. Vulvar cancer and its precursors are less frequent than their cervical counterparts. The cancers associated with lichen sclerosus or lichen planus tend to occur in older women and have a worse prognosis, while the HPV associated is often seen in younger women, and smokers, with other lesions of the anogenital tract and immunodepression.

WLHIV are at increased risk for developing vaginal intraepithelial neoplasia, which appears at an early age as compared to HIV-negative women. Infected women display the lesion during ART, are frequently smokers, and the disease may be multifocal and multicentric. The survival is similar for women with and without HIV infection [87].

## Low urinary tract symptoms

The management of urinary symptoms in women with HIV is relevant for individual patients and public health since the low urogenital tract is a vector for HIV infection [88]. Post-menopausal WLHIV have a significant increase to suffer severe urogenital symptoms as evaluated with the Menopause Rating Scale [54]. They also have a high rate

of bladder dysfunction and opportunistic infections that with appropriate treatments may currently reduce their prevalence [89]. Several factors may be involved in micturition disturbances, including urinary tract inflammation, side effects or toxicity of antiretroviral treatments, opportunistic infections, menopause-related low urinary tract changes, and neurologic effects of HIV [90].

The reduced immune function in HIV patients favors the urinary tract infection by common uro-pathogens and less common bacteria. It seems that urinary infections are more prevalent among women than men living with HIV, and more frequent in long-term survivors [91]. Urinary infections are frequent among people living with HIV in under-developed countries, having rates of 12.8% in Ethiopia, 25% in Nigeria, and 65% in Cameroon **[**92-94**].** In WLHIV virologically suppressed, the risk of urinary infection increases with age, increased body mass index, and being parous peri- postmenopausal women, and not associated with HIV-related factors [89].

## Conclusions

The prognostic of HIV infection has improved with ARTs in recent years. Perimenopausal WLHIV may have increased climacteric and depressive symptoms compared with premenopausal years [95,96]. WLHIV who report severe symptoms have greater odds of low ART adherence, and CD-4 count [97,98]. Psychological factors and lifestyle may influence disease risks and the immune system. WLHIVwith CD4 counts inferior to 200 cells/$mm^3$ report more symptoms and complications than those with counts higher than 500 cells [95].

Despite the increase in scientific knowledge concerning HIV infection gathered during recent years, the received health care by peri- and postmenopausal women are still very heterogeneous depending on socioeconomic factors, the female social role, differences in the health care systems, co-morbidity, addictive drug-related factors, and adherence to the ART. WLHIV may benefit and deserve specialized healthcare concerning the low genitourinary tract and early menopause risks. Future research are needed to evaluate:

(i) The balance between the benefits and risks of menopause hormone therapy in peri- and early postmenopausal WLHIV compared to those without HIV, both at the low genitourinary tract level and on systemic outcomes.

(ii) The immune status and long-term menopause-related risks according to ART compliance, the duration of HIV infection, lifestyle, and addictive drug consumption.

(iii) The balance between benefits and risks of ART to cardiovascular, bone metabolism and osteoporosis, and sarcopenia and dynapenia.

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