

The menopause transition in women living with HIV: current evidence and future avenues of research

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Abstract

As the life expectancy of people living with HIV improves as a result of antiretroviral therapy, increasing numbers of women living with HIV (WLHIV) are now reaching menopausal age. The menopause transition in WLHIV remains a relatively overlooked area in clinical HIV research. Whilst there is some evidence to suggest that WLHIV experience menopause at an earlier age and that they have more menopausal symptoms, there is no clear consensus in the literature around an impact of HIV infection on either timing or symptomatology of the menopause. Data are also conflicting on whether HIV-related factors such as HIV viral load and CD4 cell count have an impact on the menopause. Furthermore, menopausal symptoms in WLHIV are known to go under-recognised by both healthcare providers and women themselves.

There is likely to be a burden of unmet health needs among WLHIV transitioning through the menopause, with significant gaps in the evidence base for their care. With this in mind, we have developed the PRIME study (Positive Transitions Through the Menopause). This mixed-methods observational study will explore, for the first time in the UK, the impact of the menopause on the health and wellbeing of 1500 ethnically diverse WLHIV. In establishing a cohort of women in their midlife and following them up longitudinally, we hope to develop a nuanced understanding of the gendered aspects of ageing and HIV, informing the provision of appropriate services for WLHIV to ensure that they are supported in maintaining optimal health and wellbeing as they get older.

Keywords: HIV, women, ageing, menopause

Introduction

Of the 37 million people currently living with HIV globally, half are women (www.unaids.org, accessed 07 January 2016). Despite this, there remains a paucity of data relating to the reproductive and post-reproductive health of women living with HIV (WLHIV) [1].

Improvements in survival due to antiretroviral therapy (ART) have resulted in successfully treated HIV-positive individuals now having a near normal life expectancy, and a shift in the age distribution of people living with HIV [2,3]. The transformation of HIV into a chronic medical condition means that co-morbid conditions and other age-related events are now of increasing importance in clinical HIV practice; among women, these events include the menopause. Approximately 8700 women of potentially menopausal age (between 45 and 56) attended for HIV-related care in the UK in 2014, a six-fold increase over a 10-year period (Z Yin, Public Health England, personal communication). Based on the age distribution of HIV-positive women attending for HIV care in 2013, a total of 10,000 women are likely to reach potentially menopausal age in the next 10 years (Z Yin, Public Health England, personal communication) [4].

Overview of natural menopause

Natural menopause is defined as 'the permanent cessation of menstruation resulting from the loss of ovarian follicular activity', in the absence of other physiological or pathological causes [5]. The average age at natural menopause in the UK is 52 years [6], although there is considerable geographical variation, with age at natural menopause lowest among women from African, Latin American, Asian and Middle Eastern countries [7]. The transition to menopause is often accompanied by a range of physical and

psychological changes, with 85% of women reporting symptoms such as hot flushes, sleep disturbance or mood changes [8]. According to a recent large American cohort study, the median duration of vasomotor symptoms is longer than previously thought at 7.4 years, continuing for an average of 4.5 years beyond final menstrual period [9]. However, it is important to note that the menopause is a complex *biosocial* phenomenon, where factors such as ethnicity and socioeconomic status affect reporting, duration and experience of symptoms [9–11]. Despite this variation across sociocultural contexts, menopausal symptoms have consistently been shown to impact negatively upon women's perceived health, their quality of life, and their role performance both at work and within relationships [12–14].

HIV and the menopause

There are several reasons why we may expect the menopause transition to be different in WLHIV. First, gonadal dysfunction is well-described in men living with HIV, even in the highly active antiretroviral therapy (HAART) era [15]. Gonadal function is relatively understudied in WLHIV, however, an analysis of data from the Women's Interagency HIV Study (WIHS) found that HIV-positive women were more likely to have lower levels of anti-mullerian hormone (a biological marker of ovarian reserve), largely explained by lower CD4 counts [16]. The pathophysiology underlying ovarian dysfunction in WLHIV is likely to be similar to that underlying hypogonadism in men, with possible factors including the effects of opportunistic infection and the virus itself on the ovaries and the pituitary gland [15]. Furthermore, given that HIV is increasingly understood to be associated with persistent inflammation, we can hypothesise that this may affect the neuroendocrine axis. HIV-related effects on the ovaries or neuroendocrine axis may alter both the natural history and symptomatology of menopause in WLHIV, especially in the context of other contributing factors such as substance misuse, lower socioeconomic status and non-Caucasian ethnicity.

Secondly, there may be an additive effect of oestrogen depletion to the already increased risk of dyslipidaemia, osteoporosis and

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cardiovascular disease in WLHIV [17]. Finally, transitioning through the menopause in the context of chronic illness may present difficulties in determining aetiology of symptoms, with evidence suggesting that menopausal symptoms in WLHIV go under-recognised by both healthcare providers [18] and women themselves [19]. Moreover, WLHIV face the additional challenge of managing menopausal symptoms whilst living with a chronic illness requiring careful management and monitoring.

Current evidence

Data on the association between HIV and earlier age at menopause is conflicting. Several studies, including one of the very few to be conducted in Europe, have reported a median age at menopause younger than 52, with ages ranging from 47.5 to 50 years, suggesting that WLHIV may transition through menopause at an earlier age than their HIV-negative counterparts [20–25]. However, the only studies including an HIV-negative comparison group have reported similar ages at menopause in both HIV-positive and HIV-negative women [25,26]. In terms of predictors of age at menopause in WLHIV, again data are conflicting with some authors reporting no association between age at menopause and HIV-related factors such as HIV viral load, CD4 cell count and the use of ART [20,22], and others reporting current low CD4 cell count as a risk factor [24,26,27].

Relatively few studies exist on the symptomatology of the menopause in WLHIV. Lui-Filho *et al.* [28] reported no association between HIV status and a range of menopausal symptoms including hot flushes and vaginal dryness. However, other authors have reported that HIV-positive serostatus is associated with increased menopausal symptoms including hot flushes [29], other vasomotor symptoms [20,23], sexual dysfunction [20], and mood changes [23,30]. Again, there is little consensus on the relationship between cell count and HIV viral load, and menopausal symptoms with two studies reporting no association [21,29] and others demonstrating an association between higher CD4 cell count and increased vasomotor symptoms [28,31].

Finally, given the immunomodulatory effects of oestrogen, the impact of the menopause transition and consequent oestrogen depletion on the natural history of HIV is of interest. However, only three studies have looked at this, finding no evidence of an effect of menopausal status on either CD4 cell count decline after HIV seroconversion [32], or response to ART [33,34].

Gaps in evidence

In view of the conflicting literature on HIV and both natural history and symptomatology of the menopause, further research is warranted in this area. Of note, the overwhelming body of work has emerged from the United States and South America. Findings from these studies may not be applicable in settings such as sub-Saharan Africa and Europe, where patient cohorts may differ in terms of ethnicity, comorbidity, substance misuse, socioeconomic status and healthcare access.

Current UK guidelines on management of the menopause recommend that menopausal women be given adequate information on symptomatology, lifestyle modification and treatment options including hormone replacement therapy (HRT) [35]. HRT can be offered to alleviate vasomotor symptoms and low mood that arise as a result of the menopause [34]. However, there are notable gaps in the evidence base around the clinical support required for WLHIV experiencing the menopause transition. This includes a lack of information on: long-term safety and efficacy of HRT; drug interactions between HRT and ART; the potential role of psychosocial interventions; and the impact of the menopause transition on WLHIV's quality of life and their ability

to engage with health-sustaining behaviours such as adherence to ART and retention in HIV care. Finally, there remains an absence of qualitative literature on women's experience of reproductive ageing in the context of HIV.

The PRIME study

With these gaps in mind, we designed the PRIME study (Positive Transitions Through the Menopause, www.ucl.ac.uk/prime-study), a mixed-methods observational study funded by the UK's National Institute of Health Research (NIHR). Our overarching aim is to explore, for the first time in the UK, the impact of the menopause on the health and wellbeing of WLHIV. The specific objectives of the study are (amongst WLHIV):

1. To estimate the prevalence of menopause (stratified by age) and menopausal symptoms.
2. To explore factors associated with earlier age at menopause and increased menopausal symptoms.
3. To explore the association between both menopausal status and symptoms, and: (i) mental health, (ii) sexual function, (iii) quality of life, (iv) adherence to ART, (v) attendance for HIV care, and (vi) condom use.
4. To explore the mechanisms by which the menopause may impact upon engagement with HIV care and wellbeing.
5. To describe the current management of menopausal symptoms in the UK and identify areas of clinical need.

We aim to recruit 1500 WLHIV aged between 45 and 60 from National Health Service (NHS) HIV clinics across the UK. The study comprises self-completed paper questionnaires, collection of clinical data, and semi-structured interviews with a proportion of women. Furthermore, we are seeking consent for ongoing follow-up, thereby establishing a unique cohort of ethnically diverse women ageing with HIV. This will allow the longitudinal study of the effects of ageing, specifically the menopause, on the longer-term health and wellbeing of WLHIV.

Conclusion

There remains a paucity of data on HIV and the menopause, particularly within Europe and sub-Saharan Africa. Whilst there is some evidence to suggest that WLHIV experience menopause at an earlier age and that they experience a greater symptom burden than women without HIV, there is no clear consensus around the impact of HIV on either timing or symptomatology of the menopause in the literature. Little is known about predictors of menopausal symptoms within this group, nor of the impact of menopausal symptoms on women's wellbeing and ability to engage with health-sustaining behaviours. Furthermore, menopausal symptoms in WLHIV may be under-recognised by healthcare providers and by women themselves, and there are few data on symptom management within this population.

There is likely to be a burden of unmet health needs among WLHIV women transitioning through menopause. The PRIME Study is a mixed-methods observational study that will allow exploration of the impact of the menopause on health and wellbeing among an ethnically diverse cohort of WLHIV in the UK. We hope that this study will contribute to a more nuanced understanding of the gendered aspects of ageing and HIV, informing the provision of appropriate services for WLHIV to ensure that they are supported in maintaining optimal health into their post-reproductive years.

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