

The impact of the menopause transition on the health and wellbeing of women living with HIV: a narrative review

Authors: Shema TARIQ^a, Valerie DELPECH^b, Jane ANDERSON^c

^a Research Department of Infection and Population Health, University College London, Mortimer Market Centre, Off Capper Street, London, WC1E 6JB, UK. Email s.tariq@ucl.ac.uk

^b Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK. Email Valerie.Delpech@phe.gov.uk

^c Centre for the Study of Sexual Health and HIV, Homerton University Hospital, Homerton Row, London E9 6SR, UK. Email janderson@nhs.net

Correspondence to:

Dr Shema Tariq

Research Department of Infection and Population Health

University College London

Mortimer Market Centre

Off Capper Street

London WC1E 6JB

Email: s.tariq@ucl.ac.uk

ABSTRACT

Improvements in survival due to advances in antiretroviral therapy (ART) have led to a shift in the age distribution of those receiving HIV care, with increasing numbers of women living with HIV (WLWHIV) reaching menopausal age. We present a narrative literature review of 26 studies exploring the menopause transition in WLWHIV, focusing on: (1) natural history (2) symptomatology and management, and (3) immunologic and virologic effects.

Data are conflicting on the association between HIV and earlier age at menopause, and the role of HIV-specific factors such as HIV viral load and CD4 count. There are some data to suggest that WLWHIV experience more vasomotor and psychological symptoms during the menopause than HIV-negative women, and that uptake of hormone replacement therapy by WLWHIV is comparatively low. There is no evidence that menopause affects either CD4 count or response to ART, although there may be increased immune activation in older WLWHIV.

We conclude that menopause in WLWHIV is a neglected area of study. Specific information gaps include qualitative studies on experiences of reproductive ageing; data on the impact of the menopause on women's quality of life and ability to adhere to health-sustaining behaviors; as well as studies investigating the safety and efficacy of pharmacological and psychosocial interventions. There is likely to be a burden of unmet health need among this growing population, and better data are required to inform optimal provision of care, supporting WLWHIV to maintain their health and wellbeing into their post-reproductive years.

Word count: 2065

Keywords:

HIV, women, menopause

1. INTRODUCTION

In 2014, approximately 36.9 million people were living with HIV globally, of whom over half were women. (<http://www.unaids.org>, accessed 07 January 2016). Advancements in antiretroviral therapy (ART) have resulted in significant improvements in survival, such that people with well-controlled HIV may expect a near normal life expectancy.(1) Increasing coverage of ART has therefore led to a shift in the demographic profile of the HIV epidemic, reflected in increasing HIV prevalence rates among older people.(2) In 2014 nearly 25,100 people aged 50 and over attended clinical services for HIV-related care in the United Kingdom (UK), a four-fold increase since 2005. Approximately 8700 women of potentially menopausal age (i.e. between 45 and 56 years) attended for HIV-related care in the UK in 2014 (Zheng Yin, Public Health England, personal communication, 26/02/16). Based on the observed age distribution of women attending for HIV care in the UK in 2013, a total of 10,000 women are likely to reach potentially menopausal age in the next ten years (Zheng Yin, Public Health England, personal communication, 25/02/2016).(3)

A consequence of living longer with HIV is the increased likelihood of developing age-related conditions. For women living with HIV (WLWHIV) entering their midlife, this includes transition through the menopause. In the shorter term, it is known that the menopause transition is frequently associated with a range of physical and psychological changes. Approximately 85% of women report symptoms such as hot flushes, sleep disturbance and mood changes,(4) with vasomotor symptoms lasting a median duration of 7.4 years.(5) Menopausal symptoms impact negatively upon women's quality of life, their role performance at work, and their relationships.(6, 7) Furthermore, the loss of the protective effects of estrogen brings an attendant risk of longer-term conditions such as dyslipidemia, osteoporosis and cardiovascular disease, which is likely to be of particular significance for WLWHIV as the risk of developing these conditions is elevated in the context of HIV infection.(8)

Gonadal dysfunction is well-described in HIV-positive men, and ovarian dysfunction has been reported in WLWHIV.(9) The mechanisms for this remain unclear but may include: (i) direct effects of the virus itself, (ii) the effects of chronic inflammation on the neuroendocrine axis, (iii) effects of ART, and (iv) co-existing factors such as smoking, low body mass, or substance misuse. This may alter the natural history and/or symptomatology of the menopause in WLWHIV. Transitioning through the menopause in the context of chronic illness may present additional challenges in terms of ascertaining symptom etiology, with evidence to suggest that menopause-related symptoms in WLWHIV are under-recognized by healthcare providers.(10)

We present a narrative review of literature on the menopause in WLWHIV. Although noting the growing body of literature on the effects of reproductive ageing on risk of bone disease in WLWHIV, we feel this merits a review of its own and is therefore outside the scope of this paper. Our specific objectives were to summarize data in WLWHIV on the following: (1) the natural history of the menopause, (2) symptomatology of the menopause transition and its management, and (3) the immunologic and virologic effects of the menopause transition.

2. METHODS

2.1 Data extraction

We undertook a comprehensive literature search in December 2015 using the following online databases: PubMed, Embase, CINAHL, and Web of Science. Our aim was to identify original research papers that explored menopause in WLWHIV. Search terms used to identify literature included: climacteric, menopaus*, pre-menopaus*, post-menopaus*, “pre menopaus*” and “post menopaus*”, all in combination with HIV. We applied these search terms to abstracts and title in all databases, and restricted all searches to studies in human females only. There was no date restriction for any of the searches, and studies using any methodological approach were considered. Our initial literature search identified 399 documents, of which 162 were primarily focused on the menopause in WLWHIV. We reviewed these 162 documents, excluding review papers, non-English language publications, and studies that did not focus on any of our three key research questions. In addition, bibliographies of review papers were cross-referenced and we hand-searched available abstracts for the following conferences: British HIV Association (BHIVA), Conference for Retroviruses and Opportunistic Infections (CROI), and the International AIDS Society (IAS). The final number of studies included in this review is 26.

3. RESULTS

3.1 Natural history of the menopause in women living with HIV

The average age at natural menopause in the UK is 52 years.(11) Several cross-sectional studies in WLWHIV, almost all using self-reported menstrual pattern to categorize menopausal status, have reported a younger median age at menopause, ranging from 47.5 to 50 years (Table 1).(12-15) Two prospective studies, including one of very few to have been conducted in Europe, have reported similar findings.(16, 17), suggesting that WLWHIV may experience menopause at an earlier age. However, this is not supported by the only two studies that included an HIV-negative comparison group as part of their design, neither of which found any statistically significant difference in age at menopause by HIV serostatus.(18, 19) One of these was an analysis of data from the Women’s Interagency HIV Study (WIHS), a United States (US) prospective observational cohort of women both living with, and at risk of, HIV infection.(19) It is the largest study to date to compare age at menopause in HIV-positive and HIV-negative women, and the only one to use biological markers of ovarian function.

Authors from Brazil and from the UK have reported a relatively high prevalence of menopause before 45 years of age in WLWHIV.(17, 20) The study from the UK, a small retrospective case notes review, found that 14% of 123 HIV-positive women attending their clinic aged 50 or older had experienced cessation of menstruation when they were younger than 45; half of these women had experienced premature ovarian insufficiency (POI), that is menopause at 40 years or younger.(20) This is similar to the prevalence of POI in the general UK population, which is estimated to be 7.4%.(21) Other authors have reported higher rates of POI in HIV-positive women, including 12% in a French cohort (16) and 26% in a US study, which found that POI was significantly more common in WLWHIV compared to their HIV-negative counterparts.(18)

Recognized risk factors for earlier menopause such as smoking and substance misuse have been reported in studies of menopause in WLWHIV.(16-18) Co-infection with HIV and hepatitis

C has also been shown to be associated with earlier menopause.(17) However, data on the association between direct HIV-related factors and either menopausal status or age at menopause are conflicting. Some authors have found no association with CD4 Count, HIV viral load and the use of ART,(12, 14, 19) whereas lower CD4 count has been shown to be a risk factor by others.(16-18) Evidence for a link between immunosuppression and menopause is further strengthened by data suggesting that lower CD4 count is associated with anovulatory cycles (22) and decreased levels of anti-mullerian hormone (AMH), a marker of ovarian reserve.(23) Furthermore, deranged follicle-stimulating hormone (FSH) levels have been described both in HIV infection itself and with use of ART, which may affect the diagnostic value of FSH in this group of women.(24)

3.2 Symptomatology and management of the menopause transition in women living with HIV

We identified 15 studies investigating symptomatology and management of the menopause in WLWHIV, the majority conducted in the US (Table 2). Boonyanurak et al.,(12) in their study of HIV-positive women in Thailand, found that night sweats and loss of sexual desire were more prevalent in postmenopausal WLWHIV compared to those who were premenopausal. One study has found no association between HIV-status and menopausal symptoms (including vasomotor, genitourinary and psychological symptoms),(25) whereas increased symptoms have been reported by other authors.(15, 26-29)

Vasomotor symptoms are relatively well-investigated in WLWHIV. The reported prevalence of vasomotor symptoms in HIV-positive women ranges from 64-87%, (14, 15, 25, 28-30) which is not dissimilar to the rate reported in women without HIV.(4) Higher CD4 counts appear to be associated with increased symptoms in HIV-positive women.(13, 29) HIV-infection has been found to be associated with increased prevalence, frequency and severity of vasomotor symptoms.(15, 28) Looby et al. (27) followed 66 HIV-positive and HIV-negative perimenopausal women longitudinally over a 12-month period, observing an increased severity of vasomotor symptoms in WLWHIV that persisted over time. Analyses of data from both this study and from the WIHS cohort, demonstrate an association between severity and persistence of vasomotor symptoms, and elevated levels of depression in WLWHIV.(26, 31) Another analysis of WIHS data also found that vasomotor symptoms were associated with decreased scores in cognitive measures, however there was no difference by HIV serostatus.(32)

The prevalence of psychological symptoms (including depression and anxiety) in WLWHIV during the menopause transition ranges from 38% to over 95%,(15, 25, 26, 29, 31) with the variation likely to be largely due to the use of different outcome measures and differences in populations. Although psychological symptoms such as depression are reported more frequently by women in the context of HIV regardless of menopausal status, both Ferreira et al. (15) and Looby et al. (26) report an association between HIV-infection and increased psychological symptoms around the time of the menopause even when adjusting for previous history of poor mental health. In contrast, an analysis of WIHS data on 1170 women found that although depression is more prevalent among perimenopausal women when compared to premenopausal women, that this is not related to HIV serostatus.(31)

Genitourinary symptoms are common both peri- and postmenopausally. It is estimated that the prevalence these symptoms in WLWHIV is 48-73%,(14, 15, 25, 29) with Ferreira et al. (15) reporting an association with HIV-infection. Decreased sexual function has been reported in WLWHIV at all ages, and has been shown to decline postmenopausally in women regardless of HIV serostatus.(33) Only one study has investigated dyspareunia in midlife WLWHIV, describing a prevalence of 41% in WLWHIV aged 40-60 years, although this was not significantly different to the prevalence in the HIV-negative comparison group.(34)

We found very few studies that sought to explore management of the menopause in WLWHIV, and none that assessed efficacy or safety of interventions. Small studies have revealed low rates of hormone replacement therapy (HRT) use among WLWHIV, with estimated usage ranging from 0-11%.(13, 14, 20, 30) This may be related to limited awareness of the menopause within this patient group.(30)

3.3 Immunologic and virologic effects of the menopause transition in women living with HIV

The immunomodulatory effects of estrogen is well-recognized,(35) making the effects of estrogen depletion on the natural history of HIV-infection of particular interest. We identified four studies that investigate this (Table 3). Comparing postmenopausal HIV-positive and HIV-negative women, Alcaide et al. (36) report higher levels of immune activation and microbial translocation in older WLWHIV, which appear to correlate with biomarkers of cardiovascular disease and cognitive impairment.(36) However, there is no evidence thus far of an effect of menopausal status on either CD4 count decline post-seroconversion to HIV,(37) or immunologic or virologic response to ART.(38, 39).

4. CONCLUSION

Despite the growing numbers of women living with HIV who are transitioning through the menopause, existing data is scanty and frequently contradictory. Much of the available data comes from the USA, where the populations of women affected by HIV differ from those in Europe and the UK, making comparisons across studies and data sets problematic. The influence of viral activity and immune suppression as evidenced by the HIV viral load and CD4 count respectively on ovarian function may be an important consideration on the timing of menopause, although uncertainty remains about the impact of HIV on age at menopause. As HIV and its treatments can predispose to a variety of metabolic complications, many of which are also associated with ageing, the implications of menopausal changes for women with HIV are significant. Data on best management strategies for HIV-positive menopausal women are lacking, Despite UK recommendations that HRT should be discussed and offered to menopausal women,(40) there appear to be low rates of use by women living with HIV, with the reasons underlying this unknown. Given the complexity of the lives of women living with HIV, understanding the additional impact of menopause on quality of life, and women's abilities to engage with health-sustaining behaviors including adherence to ART and retention in care, are important issues for future research. There is likely to be a significant burden of unmet health

needs among menopausal women living with HIV making a better understanding of the impact and best practice approaches to management an important priority for future investigation.

Contributors:

ST designed the literature search and drafted the first version of this article. Both ST and JA selected the final studies to be included in this review. VD provided epidemiological data from the UK. All authors critically reviewed the first version of the article and approved the final draft for publication.

Conflicts of interest:

ST has previously received a travel bursary funded by Janssen-Cilag through the British HIV Association. ST and JA are members of the steering group of SWIFT, a networking group for people involved in research in HIV and women, funded by Bristol Myers Squibb.

Funding:

ST is funded by the National Institute of Health Research (NIHR) in the form of a postdoctoral fellowship (PDF-2014-07-071). Any views expressed in this paper are those of the authors, and not necessarily those of the funders.

REFERENCES

1. Mocroft A, Lundgren JD, Sabin ML, Monforte A, Brockmeyer N, Casabona J, et al. Risk Factors and Outcomes for Late Presentation for HIV-Positive Persons in Europe: Results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). *PLoS Med.* 2013;10(9):e1001510.
2. Mahy M, Autenrieth CS, Stanecki K, Wynd S. Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates and survey data. *AIDS.* 2014.
3. Yin Z, editor Over Half of People in HIV Care in the United Kingdom by 2028 Will Be Aged 50 Years or Above. 15th European AIDS Conference; 2015; Barcelona, Spain.
4. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas.* 1992;14(2):103-15.
5. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition. *JAMA Internal Medicine.* 2015.
6. Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas.* 2009;62(2):153-9.
7. Woods NF, Mitchell ES. Symptom interference with work and relationships during the menopausal transition and early postmenopause: observations from the Seattle Midlife Women's Health Study. *Menopause.* 2011;18(6):654-61.
8. Looby SE. Menopause-associated metabolic manifestations and symptomatology in HIV infection: a brief review with research implications. *J Assoc Nurses AIDS Care.* 2012;23(3):195-203.
9. Yalamanchi S, Dobs A, Greenblatt RM. Gonadal function and reproductive health in women with human immunodeficiency virus infection. *Endocrinol Metab Clin North Am.* 2014;43(3):731-41.
10. Cejtin HE, Kim S, Taylor RN, Watts DH, editors. Assessment of menopausal status among women in the Women's Interagency HIV Study (WIHS). The XV International AIDS Conference; 2004; Bangkok.
11. The British Menopause Society. Premature Menopause 2013 [cited 2013 29 October]. Available from: <http://www.thebms.org.uk/factdetail.php?id=1>.
12. Boonyanurak P, Bunupuradah T, Wilawan K, Lueanyod A, Thongpaeng P, Chatvong D, et al. Age at menopause and menopause-related symptoms in human immunodeficiency virus-infected Thai women. *Menopause.* 2012;19(7):820-4.
13. Clark RA, Cohn SE, Jarek C, Craven KS, Lyons C, Jacobson M, et al. Perimenopausal symptomatology among HIV-infected women at least 40 years of age. *J Acquir Immune Defic Syndr.* 2000;23(1):99-100.
14. Fantry LE, Zhan M, Taylor GH, Sill AM, Flaws JA. Age of menopause and menopausal symptoms in HIV-infected women. *AIDS Patient Care STDS.* 2005;19(11):703-11.
15. Ferreira CE, Pinto-Neto AM, Conde DM, Costa-Paiva L, Morais SS, Magalhaes J. Menopause symptoms in women infected with HIV: prevalence and associated factors. *Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology.* 2007;23(4):198-205.
16. de Pommerol M, Hessamfar M, Lawson-Ayayi S, Neau D, Geffard S, Farbos S, et al. Menopause and HIV infection: age at onset and associated factors, ANRS CO3 Aquitaine cohort. *Int J STD AIDS.* 2011;22(2):67-72.

17. Calvet GA, Grinsztejn BG, Quintana Mde S, Derrico M, Jalil EM, Cytryn A, et al. Predictors of early menopause in HIV-infected women: a prospective cohort study. *American Journal of Obstetrics and Gynecology*. 2015;212(6):765 e1- e13.
18. Schoenbaum EE, Hartel D, Lo Y, Howard AA, Floris-Moore M, Arnsten JH, et al. HIV infection, drug use, and onset of natural menopause. *Clin Infect Dis*. 2005;41(10):1517-24.
19. Cejtin HE, Kim S, Taylor RN, Minkoff HL, Massad LS, Preston-Martin S, et al., editors. Menopause in women in the Women's Interagency HIV Study (WIHS). The XV International AIDS Conference; 2004; Bangkok.
20. Samuel M, Welch J, Tenant-Flowers M, Poulton M, Campbell L, Taylor C. Care of HIV-positive women aged 50 and over - can we do better? *Int J STD AIDS*. 2013.
21. Islam R, Cartwright R, editors. The impact of premature ovarian failure on quality of life: results from the UK 1958 Birth Cohort. *Human Reproduction*; 2011: Oxford University Press.
22. Clark RA, Mulligan K, Stamenovic E, Chang B, Watts H, Andersen J, et al. Frequency of anovulation and early menopause among women enrolled in selected adult AIDS clinical trials group studies. *J Infect Dis*. 2001;184(10):1325-7.
23. Scherzer R, Bacchetti P, Messerlian G, Goderre J, Maki PM, Seifer DB, et al. Impact of CD4+ lymphocytes and HIV infection on Anti-Mullerian Hormone levels in a large cohort of HIV-infected and HIV-uninfected women. *Am J Reprod Immunol*. 2015;73(3):273-84.
24. Santoro N, Arnsten JH, Buono D, Howard AA, Schoenbaum EE. Impact of street drug use, HIV infection, and highly active antiretroviral therapy on reproductive hormones in middle-aged women. *Journal of Women's Health (2002)*. 2005;14(10):898-905.
25. Lui-Filho JF, Valadares AL, Gomes Dde C, Amaral E, Pinto-Neto AM, Costa-Paiva L. Menopausal symptoms and associated factors in HIV-positive women. *Maturitas*. 2013;76(2):172-8.
26. Looby S, Shifren JL, Corless I, Pedersen MC, Grinspoon S, Joffe H. Depressive symptoms in perimenopausal women with and without hiv. *Menopause*. 2013;20 (12):1341.
27. Looby S, Shifren JL, Grinspoon S, Joffe H. Longitudinal assessment of menopause symptoms in perimenopausal women with HIV. *Menopause*. 2014;21 (12):1354.
28. Looby SE, Shifren J, Corless I, Rope A, Pedersen MC, Joffe H, et al. Increased hot flash severity and related interference in perimenopausal human immunodeficiency virus-infected women. *Menopause*. 2014;21(4):403-9.
29. Miller SA, Santoro N, Lo Y, Howard AA, Arnsten JH, Floris-Moore M, et al. Menopause symptoms in HIV-infected and drug-using women. *Menopause*. 2005;12(3):348-56.
30. Hughes CA, Yuksel N, Foisy M. A survey on the severity and management of menopausal symptoms in middle-aged HIV-infected women. *Canadian Journal of Infectious Diseases and Medical Microbiology*. 2012;23:119A.
31. Maki PM, Rubin LH, Cohen M, Golub ET, Greenblatt RM, Young M, et al. Depressive symptoms are increased in the early perimenopausal stage in ethnically diverse human immunodeficiency virus–infected and human immunodeficiency virus–uninfected women. *Menopause*. 2012;19(11):1215-23.
32. Rubin LH, Sundermann EE, Cook JA, Martin EM, Golub ET, Weber KM, et al. Investigation of menopausal stage and symptoms on cognition in human immunodeficiency virus-infected women. *Menopause*. 2014;21(9):997-1006.
33. Wilson TE, Jean-Louis G, Schwartz R, Golub ET, Cohen MH, Maki P, et al. HIV infection and women's sexual functioning. *J Acquir Immune Defic Syndr*. 2010;54(4):360-7.
34. Valadares AL, Pinto-Neto AM, Gomes Dde C, D'Avanzo WC, Moura AS, Costa-Paiva L, et al. Dyspareunia in HIV-positive and HIV-negative middle-aged women: a cross-sectional study. *BMJ Open*. 2014;4(11):e004974.
35. Gameiro C, Romao F. Changes in the immune system during menopause and aging. *Frontiers in Bioscience*. 2009;2:1299-303.

36. Alcaide ML, Parmigiani A, Pallikkuth S, Roach M, Freguja R, Della Negra M, et al. Immune activation in HIV-infected aging women on antiretrovirals--implications for age-associated comorbidities: a cross-sectional pilot study. *PLoS one*. 2013;8(5):e63804.
37. van Bentem BH, Vernazza P, Coutinho RA, Prins M. The impact of pregnancy and menopause on CD4 lymphocyte counts in HIV-infected women. *AIDS*. 2002;16(6):919-24.
38. Calvet GA, Velasque L, Luz PM, Cardoso SW, Derrico M, Moreira RI, et al. Absence of effect of menopause status at initiation of first-line antiretroviral therapy on immunologic or virologic responses: a cohort study from Rio de Janeiro, Brazil. *PLoS one*. 2014;9(2):e89299.
39. Patterson KB, Cohn SE, Uyanik J, Hughes M, Smurzynski M, Eron JJ. Treatment responses in antiretroviral treatment-naive premenopausal and postmenopausal HIV-1-infected women: an analysis from AIDS Clinical Trials Group Studies. *Clin Infect Dis*. 2009;49(3):473-6.
40. National Institute for Health and Care Excellence (NICE). Menopause: diagnosis and management. National Institute for Health and Care Excellence (NICE), 2015 12 November.

Table 1: Natural history of the menopause in women living with HIV

Reference	Aims	Sample	Design	Definition of menopause	Findings
12	To investigate age at natural menopause in WLWHIV	<ul style="list-style-type: none"> • Thailand • 268 WLWHIV • Aged ≥40 	<ul style="list-style-type: none"> • Cross-sectional • Questionnaire 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • 55 women had reached menopause • Median age at menopause=47 • Menopause associated with CDC stage but not CD4 count or HIV viral load
13	To define menopause in WLWHIV	<ul style="list-style-type: none"> • US • 101 WLWHIV • Aged ≥40 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • FSH>35 mU/ml or ≥ 6 months without menstruation and aged ≥55 years 	<ul style="list-style-type: none"> • 50% were postmenopausal • Mean age at menopause= 47
14	To examine median age at menopause and factors associated with postmenopausal status in WLWHIV	<ul style="list-style-type: none"> • US • 120 WLWHIV • Aged 40-57 • 95% African-American 	<ul style="list-style-type: none"> • Cross sectional questionnaire study 	<ul style="list-style-type: none"> • LMP ≥1 year before enrolment 	<ul style="list-style-type: none"> • 25% were postmenopausal • 26% were perimenopausal • Median age at menopause=50 • No association between menopausal status and CD4 count, HIV viral load or ART regimens.
15	To evaluate prevalence of and factors associated with menopausal symptoms in WLWHIV	<ul style="list-style-type: none"> • Brazil • 96 HIV-positive; 155 HIV-negative • Aged ≥40 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • Median age at menopause for WLWHIV=48
16	To describe the characteristics of postmenopausal WLWHIV and to identify factors associated with earlier age at menopause	<ul style="list-style-type: none"> • France • 404 WLWHIV 	<ul style="list-style-type: none"> • Cross-sectional questionnaire study with prospective follow-up 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • 17% postmenopausal at enrolment • Median age at menopause=49 • 12% reached natural menopause aged <40 • African origin, history of IDU and CD4<200 associated with earlier age at menopause

Table 1: Natural history of the menopause in women living with HIV

Reference	Aims	Sample	Design	Definition of menopause	Findings
17	To investigate age at natural menopause and its predictors in WLWHIV	<ul style="list-style-type: none"> • Brazil • 667 WLWHIV • Aged ≥ 30 	<ul style="list-style-type: none"> • Prospective observational cohort 	<ul style="list-style-type: none"> • LMP ≥ 1 year before enrolment 	<ul style="list-style-type: none"> • 27% menopause aged < 45 • Median age at menopause=48 • Younger age at menopause associated with earlier menarche, smoking, chronic hepatitis C infection, and current CD4< 50
18	To study the association between HIV infection and substance misuse, and age at natural menopause	<ul style="list-style-type: none"> • US • 302 HIV-positive; 269 HIV-negative • Aged 35-59 • 49% African American; 52% reported substance misuse 	<ul style="list-style-type: none"> • Cross-sectional questionnaire study with prospective follow-up 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • Median age at menopause in WLWHIV=46 (47 in HIV-negative women) • HIV-infection associated with menopause age < 40 • HIV-infection and substance misuse associated with being postmenopausal • Amongst WLWHIV, lower CD4 count associated with postmenopausal status
19	To compare menopause between HIV-positive and HIV-negative women in the Women's Interagency HIV Study (WIHS)	<ul style="list-style-type: none"> • US • 1062 HIV-positive; 273 HIV-negative • Aged < 55 	<ul style="list-style-type: none"> • Cross-sectional questionnaire study with serum samples 	<ul style="list-style-type: none"> • ≥ 6 months without menstruation AND FSH > 25 IU/ml 	<ul style="list-style-type: none"> • Median age at menopause in WLWHIV=47 years (48 years in HIV-negative women) • No association between HIV infection and menopause • No association between menopause and CD4 count, HIV viral load, AIDS-related illness or use of ART
20	To describe age-specific health issues in WLWHIV aged ≥ 50 years	<ul style="list-style-type: none"> • UK • 123 WLWHIV • Aged ≥ 50 • 91% on ART; 67% Sub-Saharan African origin 	<ul style="list-style-type: none"> • Retrospective notes review 	<ul style="list-style-type: none"> • Not described 	<ul style="list-style-type: none"> • 82% of women were postmenopausal • 7% had menopause 40-44; 7% had menopause < 40

Table 1: Natural history of the menopause in women living with HIV

Reference	Aims	Sample	Design	Definition of menopause	Findings
22	To obtain information on prevalence of anovulation and early menopause in WLWHIV	<ul style="list-style-type: none"> • US • 52 HIV-positive • Aged 20-42 	<ul style="list-style-type: none"> • Testing of stored serum samples 	<ul style="list-style-type: none"> • Anovulation: Progesterone level ≤ 3.1 ng/ml • Menopause: FSH >40 mIU/ml 	<ul style="list-style-type: none"> • Anovulation=48% • Early menopause=8% • Higher CD4 associated with less change in menstrual pattern
23	To describe associations between AMH levels and HIV-related factors	<ul style="list-style-type: none"> • US • 2621 HIV-positive; 941 HIV-negative 	<ul style="list-style-type: none"> • Longitudinal cohort study utilizing serum markers of ovarian function 	NA	<ul style="list-style-type: none"> • Lower CD4 count associated with lower AMH levels • In adjusted analyses HIV-infection associated with higher AMH levels
24	To assess impact of street drug use and HIV infection on reproductive hormones	<ul style="list-style-type: none"> • US • 82 HIV-positive; 15 HIV-negative • Aged 18-56 • 46% reported substance misuse 	<ul style="list-style-type: none"> • Prospective cohort study utilizing serum markers of reproductive function 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • Substance misuse and HIV-infection associated with decreased FSH levels in postmenopausal women • ART associated with higher FSH

WLWHIV, women living with HIV; LMP, last menstrual period; FSH, follicle-stimulating hormone; ART, antiretroviral therapy; IDU, injecting drug use; AMH, anti-mullerian hormone

Table 2: Symptomatology and management of the menopause transition in women living with HIV

Reference	Aims	Sample	Design	Menopause definition	Findings
12	To investigate menopause related symptoms in WLWHIV	<ul style="list-style-type: none"> • Thailand • 268 WLWHIV • Aged ≥ 40 	<ul style="list-style-type: none"> • Cross-sectional • Questionnaire 	<ul style="list-style-type: none"> • LMP ≥ 1 year before enrolment 	<ul style="list-style-type: none"> • Postmenopausal WLWHIV had more night sweats and less sexual desire than premenopausal women
13	To describe prevalence of perimenopausal symptomatology in WLWHIV	<ul style="list-style-type: none"> • US • 101 WLWHIV • Aged ≥ 40 years • 26% CD4<200; 20% not on ART 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • FSH>35 mU/ml or ≥ 6 months without menstruation and aged ≥ 55 years 	<ul style="list-style-type: none"> • Higher CD4 count associated with increased vasomotor symptoms • Higher HIV viral load associated with increased anxiety symptoms • Use of HRT=11%
14	To evaluate the prevalence of menopausal symptoms in WLWHIV	<ul style="list-style-type: none"> • US • 120 WLWHIV • Aged 40-57 • 95% African-American 	<ul style="list-style-type: none"> • Cross-sectional questionnaire study 	<ul style="list-style-type: none"> • LMP ≥ 1 year before enrolment 	<ul style="list-style-type: none"> • Symptoms in WLWHIV: vasomotor=87%, genitourinary=53% • Use of HRT=10%
15	To describe prevalence of and factors associated with menopausal symptoms in WLWHIV	<ul style="list-style-type: none"> • Brazil • 96 HIV-positive; 155 HIV-negative • Aged ≥ 40 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • Symptoms in WLWHIV: vasomotor=78%, psychological=98%, genitourinary=73% • HIV-infection associated with increased psychological, vasomotor and genitourinary symptoms
20	To describe age-specific health issues in WLWHIV aged ≥ 50 years	<ul style="list-style-type: none"> • UK • 123 WLWHIV • Aged ≥ 50 • 91% on ART; 67% Sub-Saharan African origin 	<ul style="list-style-type: none"> • Retrospective notes review 	<ul style="list-style-type: none"> • Not described 	<ul style="list-style-type: none"> • Menopausal symptoms =28% • Use of HRT=10%

Table 2: Symptomatology and management of the menopause transition in women living with HIV

Reference	Aims	Sample	Design	Menopause definition	Findings
25	To evaluate menopausal symptoms and associated factors in WLWHIV	<ul style="list-style-type: none"> • Brazil • 273 HIV-positive; 264 HIV-negative • Aged 40-60 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • Symptoms in WLWHIV: vasomotor=69%, psychological=83%, genitourinary=55% • No association between HIV status and vasomotor, psychological or genitourinary symptoms
26	To evaluate depressive symptoms and correlates in perimenopausal WLWHIV	<ul style="list-style-type: none"> • US • 33 HIV-positive; 33 HIV-negative • Aged 45-52 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • Perimenopause defined as one menstrual cycle longer in the prior 6 months, or irregular menses in ≥ 2 cycles within the past 6 months 	<ul style="list-style-type: none"> • Depression in women living with HIV=67% • HIV-infection associated with increased depression despite similar levels of prior depression • Increased depression associated with hot flush severity in both HIV-positive and HIV-negative women
27	Longitudinal evaluation of menopausal symptoms in WLWHIV over 12 months	<ul style="list-style-type: none"> • US • 33 HIV-positive; 33 HIV-negative • Aged 45-52 	<ul style="list-style-type: none"> • Longitudinal questionnaire 	<ul style="list-style-type: none"> • Perimenopause=one menstrual cycle longer in the prior 6 months, or irregular menses in ≥ 2 cycles within the past 6 months 	<ul style="list-style-type: none"> • Greater burden of hot flushes, insomnia, anxiety and depression in WLWHIV persisted at 12 months
28	To evaluate hot flush severity and related interference among perimenopausal HIV-positive and HIV-negative women	<ul style="list-style-type: none"> • US • 33 HIV-positive; 33 HIV-negative • Aged 45-52 	<ul style="list-style-type: none"> • Cross-sectional questionnaire with serum samples 	<ul style="list-style-type: none"> • Perimenopause=one menstrual cycle longer in the prior 6 months, or irregular menses in ≥ 2 cycles within the past 6 months 	<ul style="list-style-type: none"> • Hot flushes ≥ 8 days in past 4 weeks in WLWHIV=67% • HIV-infection associated with increased frequency and severity of hot flushes • FSH and estradiol levels similar in both HIV-positive and HIV-negative women

Table 2: Symptomatology and management of the menopause transition in women living with HIV

Reference	Aims	Sample	Design	Menopause definition	Findings
29	To examine the association of HIV infection, substance misuse and psychosocial stressors with menopausal symptoms	<ul style="list-style-type: none"> • US • 289 HIV-positive; 247 HIV-negative • Aged ≥ 35 • 48% African American; 30% substance misuse 	<ul style="list-style-type: none"> • Cross-sectional study 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • Symptoms in WLWHIV: vasomotor=64%, psychological=90%, genitourinary=48% • HIV-infection associated with increased symptoms • Menopausal symptoms decreased as CD4 declined • Menopause symptoms in WLWHIV associated with receipt of public benefits • Increased menopause symptoms were associated with depressive symptoms in HIV-positive and HIV-negative women
30	To evaluate the frequency and severity of menopausal symptoms in WLWHIV, and management of symptoms	<ul style="list-style-type: none"> • Canada • 31 WLWHIV • Aged 40-60 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • Based on menstrual pattern but not described 	<ul style="list-style-type: none"> • Vasomotor symptoms in WLWHIV=72% • None had taken HRT • 26% had received information about the menopause
31	To evaluate the association of menopausal stage and vasomotor symptoms with depressive symptoms in women with a high prevalence of HIV	<ul style="list-style-type: none"> • US • 835 HIV-positive; 335 HIV-negative • Aged 30-65 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • Depression in women living with HIV=38% • HIV-positive and HIV-negative women in early perimenopause at higher risk of depression • Persistent vasomotor symptoms associated with depression • Depression in HIV-positive perimenopausal women was associated with not being on ART

Table 2: Symptomatology and management of the menopause transition in women living with HIV

Reference	Aims	Sample	Design	Menopause definition	Findings
32	To examine the associations of menopausal stage, menopausal symptoms, HIV status and cognition	<ul style="list-style-type: none"> • US • 708 HIV-positive; 278 HIV-negative • Aged 30-65 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • HIV associated with poorer cognitive performance • Menopausal stage not associated with cognition • Vasomotor symptoms were associated with poorer cognitive function in HIV-negative and WLWHIV
33	To compare sexual function among HIV-positive and HIV-negative women	<ul style="list-style-type: none"> • US • 1279 HIV-positive; 526 HIV-negative • Aged ≥ 20 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • HIV-infection associated with reduced sexual function at all ages • Reduced sexual function associated with being postmenopausal in HIV-negative and WLWHIV
34	To evaluate whether dyspareunia is associated with HIV status in menopausal women	<ul style="list-style-type: none"> • Brazil • 128 HIV-positive; 178 HIV-negative • Aged 40-60 	<ul style="list-style-type: none"> • Cross-sectional questionnaire 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • Dyspareunia in WLWHIV=41%% • No association between HIV-infection and dyspareunia

WLWHIV, women living with HIV; LMP, last menstrual period; ART, antiretroviral therapy; FSH, follicle-stimulating hormone; HRT, hormone replacement therapy

Table 3: Immunologic and virologic effects of the menopause transition in women living with HIV

Study	Aims	Sample	Design	Menopause definition	Findings
36	To investigate immune activation and microbial translocation in WLWHIV of postmenopausal age	<ul style="list-style-type: none"> • US • 27 HIV-positive; 15 HIV-negative • Aged >45 	<ul style="list-style-type: none"> • Cross-sectional study using biological markers 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • HIV-infection associated with immune activation and microbial translocation
37	To determine the effect of pregnancy and menopause on CD4 counts in WLWHIV	<ul style="list-style-type: none"> • 12 European countries • 382 WLWHIV with a known interval of seroconversion 	<ul style="list-style-type: none"> • Retrospective cohort study 	<ul style="list-style-type: none"> • Not described 	<ul style="list-style-type: none"> • No difference in CD4 count 3 years post-seroconversion by menopausal status
38	To compare effectiveness of 1 st line ART between premenopausal and postmenopausal WLWHIV	<ul style="list-style-type: none"> • Brazil • 383 WLWHIV (15% postmenopausal) 	<ul style="list-style-type: none"> • Longitudinal questionnaire study with serum samples 	<ul style="list-style-type: none"> • ≥ 12 months without menstruation 	<ul style="list-style-type: none"> • No difference in CD4 or virologic response by menopausal status
39	To compare immunologic and virologic responses to initial ART by menopausal status	<ul style="list-style-type: none"> • US • 267 WLWHIV (18% postmenopausal) 	<ul style="list-style-type: none"> • Retrospective cohort study 	<ul style="list-style-type: none"> • ≥ 6 months without menstruation plus FSH >35 mIU/mL at any age 	<ul style="list-style-type: none"> • No difference in immunologic or virologic response to ART by menopausal status

WLWHIV, women living with HIV; ART, antiretroviral therapy; FSH, follicle stimulating hormone