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Review

Menopause care in women living with HIV in the UK - A review

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ABSTRACT

Advances in HIV care over the last 30 years have transformed a virtually fatal condition into a chronic, manageable one. Antiretroviral therapy (ART) has dramatically changed the outlook for people living with HIV so that most individuals with well controlled disease have a normal life expectancy. As result of this increase in life expectancy, one-third of women living with HIV are of menopausal age.

Adding to the shift in age distribution, rates of new HIV diagnosis are increasing in the over 50-year age group, likely the result of a combination of low condom use and perception of transmission risk and in women, an increased risk of HIV acquisition due to the mucosal disruption that accompanies vaginal atrophy.

Many women living with HIV are unprepared for menopause, have a high prevalence of somatic, urogenital and psychological symptomatology and low rates of menopausal hormone therapy (MHT) use. Many women experience enormous frustration shuttling between their general practitioner and HIV care provider trying to have their needs met, as few HIV physicians have training in menopause medicine and primary care physicians are wary of managing women living with HIV, in part, because of fears about potential drug-drug interactions (DDIs) between MHT and ART.

Several data gaps exist with regard to the relationship between HIV and the menopause, including whether the risk of HIV transmission is increased in virally-suppressed women with vaginal atrophy, whether or not menopause amplifies the effects of HIV on cardiovascular, psychological and bone health, as well as the safety and efficacy of MHT in women living with HIV.

Menopausal women living with HIV deserve high quality individualised menopause care that is tailored to their needs. More research is needed in the field of HIV and menopause, primarily on cardiovascular disease and bone health outcomes as well as symptom control, and strategies to reduce HIV acquisition, encourage testing, and maintain older women in care in order to inform optimal clinical management.

1. Introduction

As is the case worldwide, in the United Kingdom (UK), the age distribution of people seen for HIV care is changing, with older age groups increasing both in number and proportion. For people diagnosed age 50 years or over, this increased from 13% in 2010 to 22% in 2019, and compared with 21% in 2010, in 2019 two in five (43%) adults seen for HIV care were aged 50 years or older.[1] This number is predicted to increase further.

Women of menopausal and post-menopausal age are potentially at increased risk of HIV acquisition as a consequence of mucosal disruption and alterations in vaginal microbiota associated with vaginal atrophy,[2,3] as well as being less likely to use condoms than their younger counterparts.[4]

Data from 2019 show that of the 98,552 people accessing care, 12,503 of the approximately 30,000 women living with HIV were aged between 45 and 56 (Fig. 1) and therefore of menopausal age (J Ekajeh, Public Health England, personal communication, 18 August 2021).

As the lifespan of women with HIV increases, and life expectancy mirrors that of the general population, it is expected that most will live well into their postmenopausal years.

Data on menopause in women with HIV are lacking, and little is

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known about the relationship between HIV infection and menopause. It is important to address this relationship for the following reasons: firstly, in the short term, menopausal transition is associated with symptoms that can adversely affect quality of life, and longer term, menopause increases the risk of age-related comorbidities, such as cardiovascular disease (CVD), osteoporosis and metabolic syndrome, the risks of which are already higher in women with HIV.[5,6,7]

The purpose of this review is to explore considerations for management of menopause in women with HIV in the UK.

2. Methods

A literature search was conducted between June and December 2021 using PubMed and Google Scholar. Search terms were menopause, HIV, menopause and HIV transmission, menopause and HIV acquisition, management of menopause in HIV, HRT, safety and efficacy of MHT, menopause hormone therapy, menopause related comorbidities.

3. Results

3.1. What do we know about the relationship between menopause and HIV?

3.1.1. Does menopause occur earlier in HIV and are women with HIV more symptomatic?

Although it has been postulated that HIV infection may have an effect on ovaries and the ovarian-pituitary axis, possibly through lymphocyte activation and persistent inflammation impacting ovarian signalling, there is no clear evidence that HIV infection itself affects ovarian reserve.[8,9]

The literature is mixed as to whether HIV infection affects age of onset of menopause, with some studies reporting a 2–3 year earlier onset,[10,11] while others report a similar age to HIV negative women.[12,13] Interpretation is often difficult because of confounders such as substance misuse, smoking, ethnicity and low body mass index (BMI), which are known to be associated with earlier onset of menopause, and are more prevalent in some studied populations. Some studies report higher rates of early (before age 45), and premature (before age 40) menopause.[10,14] As early and premature menopause have important clinical implications, such as higher risk of CVD and osteoporosis, this would suggest a possible increased comorbidity burden for women with HIV who enter menopause early.

The majority of women going through menopause will have symptoms, which may continue for several years. Symptoms may be impacted by factors such as ethnicity, socioeconomic status, psychological wellbeing and BMI.[15] Again, the literature is mixed on whether women with HIV have more menopausal symptoms than HIV negative women. Some studies have shown no difference,[16] while others suggest that women with HIV have an increased prevalence of hot flushes and anxiety and depression.[17,18] Two UK studies have shown high anxiety x and depression scores in menopausal women living with HIV, and a much higher incidence of poor sexual function and dissatisfaction with their sexual function than the general population.[19,20] Of concern, many women do not seek help for their symptoms. In particular, they may be less likely to report symptoms related to the genitourinary syndrome of menopause (GSM), which in addition to causing vulvovaginal symptoms also leads to increased tissue fragility which may possibly be associated with an increased risk of HIV transmission in women not on suppressive ART.

3.1.2. Does menopause affect HIV disease progression?

Although estrogen appears to have immunomodulatory effects, there is no evidence that estrogen depletion affects CD4 count, or response to ART.[21,22]

3.1.3. Are the effects of HIV and menopause additive?

Certain comorbidities associated with menopause are also more prevalent in people living with HIV.[23,24]

CVD is a major cause of death worldwide. In the UK twice as many women are likely to die from coronary heart disease as breast cancer.[25] Estrogen deficiency in menopause is associated with an increased CVD risk through mechanisms such as altered vascular function, enhanced inflammation, and reduced nitric oxide dependent vasodilatation.[26] HIV infection itself carries a higher risk of CVD even with effective ART, probably through persistent immune activation/dysregulation, altered lipid metabolism, and the effects of some antiretrovirals (ARVs).[5,27]

Rates of CVD have been reported as higher in women with HIV compared to HIV negative women.[5] However, there are no randomised controlled trials (RCTS) comparing CVD outcomes to HIV negative women.

Postmenopausal women are at risk of reduced bone mineral density (BMD), as estrogen depletion results in higher bone resorption than formation.[28] It is hypothesized that HIV infection itself is associated with an increased prevalence of osteoporosis, as a consequence of the effects of chronic inflammation, certain ARVs, and an increased prevalence of traditional risk factors for osteoporosis.[6,29]

Increased adiposity with predominantly central distribution, insulin resistance and dyslipidaemia are more common in menopause and in women ageing with HIV, leading to an increased risk of CVD, hypertension, stroke and diabetes.[7,30]

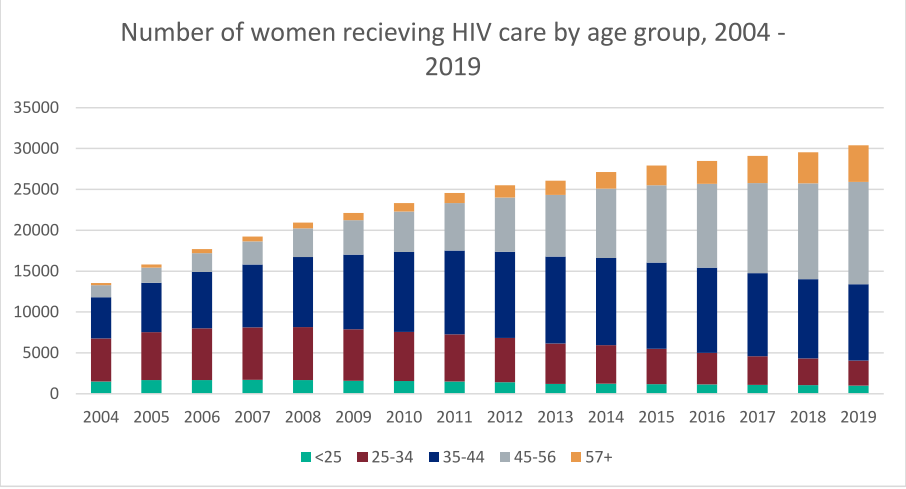

Fig. 1. Number of women receiving HIV care by age group 2004–2019 (J Ekajeh, Public Health England, personal communication, 18 August 2021).

3.2. What do we know about safety and efficacy of menopause hormone therapy (MHT) in women living with HIV?

MHT has been available for over 60 years, and has divided opinions for nearly as long. Following the publication of the Women's Health Initiative (WHI) study in 2002, which raised concerns about an increased risk of breast cancer, stroke and CVD, thousands of women stopped taking MHT, and many clinicians were subsequently reluctant to prescribe it. Since then, further re-analyses of the WHI study, and numerous new studies have demonstrated safety of MHT in younger postmenopausal women. Furthermore, important developments in the last two decades, such as transdermal estrogen preparations, and the arrival of body identical hormones such as beta(β)-estradiol and micronized progesterone have led to a reduction in MHT-associated risks (mainly venous thromboembolism [VTE] and breast cancer).

The main benefits of MHT are in menopausal symptom control and prevention of osteoporosis and fragility-related fractures. MHT has been shown to be the most effective treatment for menopausal symptoms.[31] MHT should also be considered first line for prevention and treatment of osteoporosis in women with premature ovarian insufficiency (POI), and in menopausal women below the age of 60, particularly those with symptoms.[32]

In addition, in the past 10 years a number of randomised studies have shown benefit for CVD prevention if MHT is commenced early in the menopause.[31] Data from observational studies have also shown a reduction in the risk of developing diabetes, and a slight reduction in risk of colorectal cancer.[31] However, MHT is currently not licensed for chronic disease prevention.

- **Symptom control**

Menopausal symptoms are experienced by the majority of women transitioning through menopause, and can have a significant adverse effect on quality of life. There is substantial evidence from RCTs of the beneficial effect of MHT on menopausal symptoms, in particular vasomotor symptoms, cognition, mood changes and sexual function.[33] However, there are no published data on the effect of MHT on menopausal symptoms in women with HIV.

- **MHT and physiological considerations in women living with HIV**

As previously mentioned, women with HIV are at a higher risk of CVD, osteoporosis, and metabolic syndrome, and as these conditions are also associated with ageing and menopause, menopausal women with HIV may have an increased burden of these comorbidities in comparison to their HIV negative counterparts. Data from RCTs in HIV negative women show clear benefits of MHT on prevention of osteoporosis and fragility-related fractures in current users.[34] There are also data in the literature on longer term benefits on bone health when MHT is used for a few years around menopause.[31] As the risk of osteoporosis and related fractures is higher in people living with HIV, it is reasonable to postulate that use of MHT in menopausal women with HIV could provide a long term protective effect on their bone health. However, although there is evidence of benefit in treating people living with HIV with bisphosphonates,[35] there are no data on the effect of MHT.

Within the last decade, a number of randomised studies have reported that MHT, commenced before the age of 60, or within 10 years of menopause, is associated with a reduction in atherosclerosis progression, coronary heart disease, and death from cardiovascular causes in HIV negative women.[31] Although MHT is not licensed for CVD prevention, it is important to know whether MHT has a similar effect on CVD risk in women with HIV. There are currently no RCTs comparing CVD outcomes in women with HIV compared to HIV negative women.

Observational studies have also shown a lower risk of diabetes mellitus and metabolic syndrome in MHT users.[31] There are no data on this in HIV.

In conclusion, there are currently no data on the effect of MHT on bone mineral density, CVD and symptom control in menopausal women living with HIV.

- **Risks associated with MHT use**

The main risks associated with MHT use are increased risk of VTE and a small increased risk of breast cancer.

- VTE risk

VTE risk is 2-10-fold higher in individuals with HIV than the general population.[36] This appears to be related to several factors, including chronic inflammation, immunosuppression, opportunistic infections and acquired protein C and S deficiency. However, more recent data suggest that people on effective ART with suppressed viral loads may not be at increased risk.[37]

The most important factors relating to risk of VTE with MHT are route of administration and type of hormones used. With oral estrogen, the risk of VTE is increased 2–4 fold; transdermal estrogen, by avoiding first pass metabolism in the liver, does not increase the risk above baseline.[38] In addition, body identical hormones, like β-estradiol and micronized progesterone are associated with a lower risk of VTE compared to synthetic hormones.[31,38]

- Breast cancer risk

The relationship between breast cancer and MHT is complex. Current evidence suggests that combined MHT may be associated with a slightly increased risk of breast cancer, which appears to be duration dependent, and may vary with the type of progestogen used.[39,40] There is no evidence from general cancer registries that HIV is associated with an increased risk of breast cancer, and there are no data to suggest that the risks from MHT would be any different in women living with HIV.

3.3. Pharmacological considerations for MHT and ART

There are limited data on drug-drug interactions (DDIs) between ART and MHT; however data are available on DDIs between hormonal contraception containing ethinylestradiol and synthetic progestogens, and ART.[41]

Estrogen and progestogens are predominantly metabolised in the liver by the cytochrome P450 (CYP) 3A4 pathway, and to a lesser extent by UDP-glucuronosyltransferase (UGT) pathways in the liver and gut, which are shared by a number of ARV agents. HIV protease inhibitors, cobicistat and some non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz and nevirapine, may exhibit inducing or inhibiting properties on some of these enzymes, with effects on plasma estrogen and progestogen levels. Lower hormone levels may result in a reduced impact on symptom control, and in the case of progestogens, less of an effect against endometrial hyperplasia. Higher hormone levels may be associated with an increased risk of adverse effects.

Newer ARV agents such as integrase inhibitors, are substrates of UGT1A1, and have no effect themselves on CYP or UGT pathways. In addition, newer NNRTIs like doravirine and rilpivirine, with little or no effect on CYP are unlikely to have a clinically relevant effect on the exposure of medicinal or other products metabolised by CYP enzymes.

In addition, transdermal administration bypasses first pass gut and hepatic metabolism, and so may be associated with a lower risk of DDIs, although at present there are few to no data demonstrating this.

3.4. Menopause care for women living with HIV in the UK

The primary aim of menopause care is to provide women with assessment, advice and treatment that improves their quality of life and

promotes health into the post reproductive years.[42] The British Menopause Society (BMS) vision for menopause care in the UK is that all women should have access to accurate information, and should be able to see a suitably trained healthcare professional to discuss their experience of menopause and the options available to them.

In the UK, menopause is mainly managed within primary care, with specialist gynaecology-led menopause services seeing more complex patients.

There are no specialist guidelines on the management of menopause in women with HIV in the UK.

The British HIV Association (BHIVA) Sexual and Reproductive Health guidelines recommend proactive assessment of menopausal symptoms in women living with HIV aged >45, and management in primary care in accordance with the National Institute for Health and Care Excellence (NICE) menopause guidelines.[43] These advocate a holistic and individualised approach in assessing and advising women, with particular reference to lifestyle advice, and diet modification, as well as discussion of MHT and non-hormonal and non-pharmaceutical therapies[32,44] (Table 1). It is important to be aware that there are few to no data on interactions between non-pharmaceutical menopause treatments and ARVs, and data on the safety and effectiveness of these agents are scarce for women in the general population and non-existent for women with HIV.

As noted above, in 2019 there were approximately 12,503 women with HIV of menopausal age in the UK, with a further 10,000–20,000 predicted to reach this age group in the next 10 years.

Data are sparse on how women living with HIV in the UK are managed through their menopause transition. A survey of primary care practitioners on management of menopausal symptoms in women with HIV, found that many had significant concerns, mostly related to potential DDIs with ART, and fear of missing HIV-related pathology.[45] A significant proportion thought that menopause in women with HIV should be managed in tertiary services - either within specialist menopause clinics, or by HIV specialist teams. However, over half thought that menopausal symptoms in women with HIV should be managed in primary care.

It is not known how many of these women report symptoms, or how many are treated. A study by Solomon et al. in 2020[46] found that severe menopausal symptoms were significantly associated with sub-optimal ART adherence and HIV clinic attendance; however from the published data, few women have had a menopause review, or a discussion about MHT.[19,47] Poor adherence and lack of engagement in care risk viral load rebound, disease progression and onward HIV transmission. Nearly half of women in a national study said that said they did not have enough information about the menopause and felt unprepared for it.[48] Participants described difficulties accessing appropriate advice and care for their menopausal symptoms.

The available data on MHT uptake in women living with HIV suggest that this is low with <10% using systemic MHT and only around 3% using vaginal estrogen treatments.[19]

Several gaps exist in our knowledge with respect to menopause and MHT in women with HIV:

- Data on DDIs between ART and MHT are limited
- There are no data on the effectiveness of MHT on menopausal symptoms in women with HIV or on CVD, mental or bone health outcomes
- There are no data on safety of MHT in women with HIV with regard to VTE or breast cancer risk
- Few data exist on sexual function in menopausal women with HIV. However, from the available data, the prevalence of sexual dysfunction is high and use of systemic or topical estrogen very low. Women are often embarrassed about these symptoms and may not volunteer information. It is therefore important to specifically ask about urogenital symptoms and sexual function.

Most HIV clinicians lack experience in the management of menopause; fortunately, however, in recent years more are training in menopause, and a number of specialist HIV menopause clinics have been set up in the UK.

As previously stated, apart from adverse effects on quality of life, menopause may potentiate chronic diseases such as CVD, osteoporosis, hypertension and diabetes. BHIVA guidelines recommend CVD risk assessment for people >40 years using the QRISK® tool. Bone fracture risk assessment using FRAX® is recommended in people aged >50 years, post-menopausal women and other high-risk individuals, with DEXA scanning where indicated.[49] However, these assessments are unvalidated in people living with HIV, and indeed, a recent study by Mazzitelli et al. suggested that FRAX® scores do not predict the presence of osteoporosis in over 50 year olds living with HIV.[50] In addition, suboptimal assessment of menopausal status could underestimate CVD and fracture risk in this group of women.

4. Conclusions and recommendations

Forty years since HIV was first identified, women on effective ART are living longer and healthier lives. It is predicted that, like their HIV negative counterparts, they will spend more than 1/3 of their lives post-menopause.

Currently, menopausal women living with HIV in the UK are caught between primary care, gynaecology and HIV services for their menopause care. Most HIV physicians are not trained in menopause medicine, and primary care physicians are wary of potential DDIs between MHT and ART, and of missing HIV-related pathology.

There are no specific specialist guidelines for the management of menopause in women with HIV, but we recommend the following:

- A comprehensive model with provision of individualised care is required for optimising menopausal management in women with HIV. This may be achieved by establishing close links and referral pathways between primary care, gynaecology and HIV centres. Consideration should be given to training more HIV clinicians in menopause care and to developing specialist menopause clinics within HIV services
- Research into the effects of menopause on cardiovascular risk, bone and mental health and other comorbidities is crucial to address data gaps and to develop an evidence base to inform the development of specialist guidelines
- Women of perimenopausal age should be routinely asked about their menstrual cycles and the presence of menopause symptoms at HIV follow up
- Screening for mental health and sexual difficulties should be part of routine consultations

Table 1
Non-hormonal and non-pharmaceutical treatments for menopause symptoms[a].

Non-hormonal treatments
Clonidine
Selective serotonin re-uptake inhibitors (SSRIs), e.g. fluoxetine, paroxetine, citalopram, sertraline
Serotonin-noradrenaline re-uptake inhibitors (SNRIs), e.g. venlafaxine, desvenlafaxine
Gabapentin
Non-pharmaceutical treatments
Phytoestrogens, e.g. isoflavones
Herbal treatments, e.g. Black cohosh, Red clover, St John's wort[b]
Behavioural Therapies
Cognitive Behavioural Therapy
Hypnotherapy

[a] Data on effectiveness are mixed.
[b] St Johns wort should not be co-administered with ARVs metabolised via the CYP pathway due to potential for reduced plasma ARV concentrations.

- Screening for CVD and bone health should be in line with current guidelines. Screening for cancer and other conditions should be performed in accordance with general population guidance where HIV-specific guidance is unavailble
- Women should be given information that enables them to make informed choices about the use of MHT and topical estrogen, and have access to services that provide these. As a general rule, transdermal estrogen and body identical hormones are preferred in women living with HIV, because of their potentially better metabolic profile and lower risk of VTE. Non-HIV physicians seeking advice on potential DDIs between ARVs and MHT should consult an HIV clinician; the Liverpool HIV Drug Interactions website (https://www.hiv-druginteractions.org) is an extremely useful resource. Topical estrogen use should be encouraged in women experiencing symptoms of GSM where this is not contraindicated, as well as the use of vaginal moisturizers and lubricants where necessary to optimize vaginal health
- It is crucial to ensure that menopausal symptoms are properly controlled and strategies to retain women in care are identified and implemented to prevent the consequences of viral rebound
- Safety and efficacy of non-hormonal/non-pharmaceutical and behavioural therapies should be discussed. Until more data are available on the safety and effectiveness of non-pharmaceutical preparations such as herbal treatments and phytoestrogens in women with HIV, we would not recommend their use. In particular, St Johns wort should not be used due to potential interactions with ARVs
- Women should be advised of the importance of optimising their overall health by prioritising diet, exercise and mental well-being as well as smoking cessation and reducing alcohol intake where appropriate. Advice on recommended daily dietary calcium intake and vitamin D supplementation, if required, should be part of the consultation. Access to physiotherapy for pelvic floor rehabilitation, and advice on appropriate exercises to improve bone density and muscle strength should be part of their holistic management

Menopausal women deserve high quality individualised care that is tailored to their needs, and this is also the case for women with HIV. More research is needed in the field of HIV and menopause, primarily with regard to symptom control, CVD and bone health outcomes in order to inform optimal clinical management.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Nneka Nwokolo is a full-time employee of ViiV Healthcare. Dr Bojana Dragovic has received sponsorship for conference attendance from Gilead Sciences Ltd and ViiVHealthcare. Prof Janice Rymer has no conflicts of interest to declare.

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