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Original article

POST REPRODUCTIVE HEALTH

Post Reproductive Health
0(0) 1–5
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DOI: 10.1177/2053369119838737
journals.sagepub.com/home/prh
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Experience of hormone replacement therapy in postmenopausal women living with HIV

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Abstract

Objective: To assess the uptake of hormone replacement therapy in women living with HIV (WLHIV) in particular acceptability, response to treatment and compliance.

Study design: Retrospective review of menopausal women attending a HIV medical gynaecology clinic in a tertiary referral London Hospital between 1 January 2011 and 31 December 2016.

Main outcome measures: Patient demographics, presenting symptoms, uptake of hormone replacement therapy, type of hormone replacement therapy used and bone density assessment findings at presentation.

Results: Seventy-three HIV patients were evaluated. Of them 64 (87%) were of black ethnicity and 9 (13%) were of white ethnicity. The commonest presenting complaints were vasomotor symptoms (40/73, (55%)) followed by low mood/irritability (20/73, (27%)). When offered hormone replacement therapy, this was accepted by 28/53 (52%) in WLHIV. The commonest regimen prescribed was transdermal oestradiol/micronised progesterone. A total of 22/24 (91%) women of black ethnicity reported good symptom control if they had started hormone replacement therapy, with 4/24 (17%) subsequently discontinuing it; 3/4 (75%) of white women reported good symptom control with hormone replacement therapy, with no one discontinuing it. The commonest reason for discontinuation was irregular bleeding. Of WLHIV who had a bone density assessment, 15/25 (60%) had osteopenia while 2/25 (8%) had osteoporosis.

Conclusion: Our data show that only around 50% WLHIV accepted hormone replacement therapy when offered and a high proportion of these women discontinued it. Further research is needed to explore the reason leading to low uptake and high rates of stopping hormone replacement therapy. In addition, there is a need to increase awareness of the benefits of hormone replacement therapy in WLHIV both in the context of preventing osteoporosis and menopausal symptom management.

Keywords

Hormone replacement therapy, menopause, osteoporosis

Introduction

A total of 88,769 people are living with HIV access specialist care every year in the UK. A third of these are women with one in three aged over 50, therefore, nearing or having gone through the menopause.[1]

Anti-retroviral therapy (ART) has transformed HIV into a chronic condition where women living with HIV (WLHIV) have a life expectancy similar to HIV negative women.[2] As a result, there is increasing focus on the ramifications of HIV in advancing age, with HIV and ART potentially having a long-term effect on cardiovascular disease, bone health and cognitive impairment.[2] There has, however, been little research on the effects of HIV on the menopause, in particularly the uptake of hormone replacement therapy (HRT) by women with HIV or the impact of HIV on the sequelae of the menopause including quality of life.[3]

There are conflicting data as to whether WLHIV have an earlier onset of menopause due to potential confounding risk factors such as drug use, concurrent chronic hepatitis C infection, smoking and low

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socioeconomic status, which all predict an early menopause.[4] Other studies show that women on ART had an earlier onset of menopause, with the higher CD4 cell counts and more severe menopausal symptoms.[5]

Tariq et al. reported one of the largest studies looking at the impact of the menopause on the health of WLHIV (PRIME Study). Approximately half of the study participants indicated they did not have sufficient information about the menopause, leaving many feeling under-prepared. In addition, the PRIME study showed that the use of HRT to improve menopausal symptoms was low in WLHIV.[6,7]

In addition, observational studies have reported a higher prevalence of low bone mass density with higher rates of bone loss, particularly with women on ritonavir-boosted inhibitor regimes having increased osteoclast numbers.[8] Similarly, Grigsby et al. demonstrated that patients on tenofovir were found to have changes in their gene expression implicating the loss of osteoblast function, leading to reduced bone mineral density.[9]

Method

This was a retrospective observational study. We reviewed the electronic and paper records of patients attending a specialist medical gynaecology clinic for WLHIV at a central London teaching hospital. We analysed patient demographics, presenting symptoms, uptake of HRT, the type of HRT used, bone density at presentation by DEXA scan and the short-term patient outcomes.

Data were collected on patients attending between 1 January 2011 and 31 December 2016. Data were extracted at their first appointment and at six months follow-up. Menopause was classified by age as premature (<40 years (yrs)), early (40–45 yrs) and natural (>45 yrs). Odds ratios were calculated to test the difference in proportions along with their 95% confidence intervals.

Results

Of the 579 WLHIV referred to the medical gynaecology clinic for WLHIV during the time period, 73 (12%) were postmenopausal and were included in the study. The mean (±SD) age at presentation for menopausal WLHIV was 47 yrs (±10.32) with a median age of 46 yrs (range of 36–53 yrs). A total of 14/73 (19.2%) were nulliparous, while 59/73 (80.8%) were multiparous. The ethnicity of the patients is presented in Table 1.

A total of 71/73 WLHIV (97%) were on ART while 69/71 (97%) of WLHIV had an undetectable HIV viral load on treatment as defined by a plasma HIV RNA <50 copies/mL. The median (interquartile range) current CD4 cell count was 630/μL (435,780), with the nadir and closest CD4 cell count to their menopausal diagnosis being 259/μL (111,369) and 630/μL (428, 780), respectively. Two WLHIV were naïve to ART and had a HIV RNA of 177 and 564 copies/mL and CD4 cell counts of 667/μL and 685/μL, respectively.

Of the WLHIV who had bone mineral density assessment, 15/25 (60%) had osteopenia and 2/25 (8%) had osteoporosis while 8/25 (32%) had normal bone density.

The most common presenting menopausal symptoms were vasomotor (40/73 = 55%), followed by low mood or irritability (20/73 = 27%) as shown in Table 2.

A total of 31/73 (42%) WLHIV presented with premature ovarian insufficiency (POI) or early menopause as shown in Table 3.

As shown in Table 4, 34/73 (47%) of the HIV patients were on ritonavir boosted protease inhibitor and/or tenofovir ART, whereas 39/73 (53%) were either on no treatment or non-ritonavir boosted protease inhibitor and/or tenofovir-based ART.

Table 1. Ethnic breakdown of WLHIV.

Ethnicity	Number of patients (%)
Black African	56 (77)
Black Caribbean	4 (5)
Black British	4 (5)
White British	2 (3)
White other	7 (10)
Total	73 (100)

Table 2. Presenting symptoms reported by menopausal HIV patients.

Presenting complaint	HIV patients N (%)	95% CI for the proportions
Vasomotor	40/73 (55)	43–66%
Low mood	20/73 (27)	18–39%
Insomnia	3/73 (4)	1–12%
Urinary symptoms	4/73 (5)	2–13%
Vaginal dryness	16/73 (21)	13–33%
Low energy	9/73 (12)	6–22%
Low libido	17/73 (23)	14–35%
Mood swings	15/73 (20)	12–32%
Headache	4/73 (5)	2–13%
Joint pain	12/73 (16)	9–27%
Breast tenderness	0 (0)	
Hair loss	1/73 (1.4)	0.3–7%
Dyspareunia	4/73 (5)	2–13%

A total of 48/73 (65%) of WLHIV were offered HRT for control of their menopausal symptoms, and of these only 28/48 (58%) accepted HRT. Of the patients with black ethnicity, 24/39 (61%) accepted HRT compared to 4/6 (66%) with white ethnicity ($p = 0.81$; 95% CI: 0.13–4.92). Of the HIV patients with black ethnicity, 22/24 (91%) reported good symptom control with 4/24 (17%) of those patients subsequently discontinuing it. This is compared to 3/4 (75%) of the white population having good symptoms control with no women discontinuing it as seen in Table 5.

The most common reason for discontinuation was irregular bleeding. Estrogen was up titrated in 16/28 (58%) in the HIV patients. The most common regimen prescribed was continuous or sequential transdermal oestradiol (patch or gel) plus micronised progesterone, 19/28 (68%) in HIV group.

Table 3. Number of patients who presented with menopausal symptoms in each age group premature ovarian insufficiency (<40), early menopause (40–45) and natural menopause (>45).

Age (years)	HIV N (%)	95% CI for the proportions
<40	11/73 (15%)	8–25%
40–45	20/73 (27%)	18–39%
>45	42/73 (58%)	45–69%

Discussion

The number of WLHIV, entering the menopause transition is on the rise and there is progressively more evidence emerging to suggest that these women are not satisfactorily cared for in terms of their menopausal symptoms.[10,11] A recent study by Chirwa et al. suggested primary care practitioners (PCPs) have limited knowledge, experience and confidence in dealing with menopausal symptoms in these women.[3] In the PRIME study 2018, over 95% of PCPs felt confident managing menopausal women in general. However, only 46% reported confidence in managing menopause-related symptoms in WLHIV. In addition the survey reported a very low uptake of HRT with only 8% of symptomatic menopausal WLHIV reported currently using HRT. Moreover, there is lack of information, as to how women with HIV respond when offered HRT and how adherent they are to treatment.

Our study is one of the first studies exploring acceptability and compliance with HRT in WLHIV. The study included a relatively small sample size. We believe, however, it provides useful information on the

Table 4. Type of ART.

Antiretroviral therapy (ART)	Number of patients	ART type
Darunavir/ritonavir	*18*	Ritonavir boosted protease inhibitor and/or tenofovir containing ART N=34
Atazanavir/ritonavir	*9*	
Etravirine/raltegravir/darunavir/ritonavir	*1*	
Didanosine/abacavir/atazanavir/ritonavir	*1*	
Emtricitabine/tenofovir/efavirenz	*5*	
Efavirenz	*5*	Without ritonavir or tenofovir containing ART N=39
Nevirapine	*18*	
Other	*14*	
No treatment	*2*	
Total	*73*	*73*

Table 5. Acceptability of HRT based on ethnicity.

WLHIV black ethnicity	WLHIV white ethnicity	p value (95% CI)
Declined HRT n/number offered (%) 15/39 (38%)	Declined HRT n/number offered (%) 2/6 (33%)	0.81 (0.20–7.68)
Accepted HRT n/n offered (%) 24/39 (61%)	Accepted HRT n/n offered (%) 4/6 (66%)	0.81 (0.13–4.92)
Reported good symptom control n/n started HRT (%) 22/24 (91%)	Reported good symptom control n/n started HRT (%) 3/4 (75%)	0.43 (0.04–4.52)
Discontinued HRT n/n started HRT (%) 4/24 (17%)	Discontinued HRT n/n started HRT (%) 0/4	0.67 (0.09–43.63)

uptake and experience with HRT in WLHIV. Our data suggest that WLHIV did not readily accept HRT when offered with some discontinuing it once started, despite a significant improvement in their symptom control. The reasons for this are likely to be multifactorial. WLHIV are often on polypharmacy and there may be a reluctance on their part to commence additional medications due to pill burden and the risk of side effects. Social factors may contribute to the reduced acceptability, uptake and compliance with HRT in WLHIV.[10] At times, menopausal symptoms may be difficult to distinguish from the symptoms of HIV and therefore women may not be present for treatment. WLHIV may feel inclined to focus more on HIV-related issues, rather than the potential risks of osteoporosis and cardiovascular sequelae of the menopause, seeing them as minor problems.[10,12–16] Menopausal WLHIV were found to have a high prevalence of low bone mineral density. As described in the literature this may be due to the effects of ART on osteoclasts, the change in gene expression of osteoblast function, or from HIV-related illness.[4,9]

Use of HRT in WLHIV has been further affected by concerns over interactions between anti-viral therapy and HRT.[3] There is a paucity of data on the interactions between HRT and ART in women living with HIV. However, there are data on the interactions between ART and hormonal contraception.[17] Ideally, data obtained from interactions between ART and hormonal contraceptive preparations containing potent synthetic oestradiol combined with synthetic progestogens should not be directly extrapolated to HRT preparations containing oestradiol. While the former may shed light on potential interactions in this context, further research is needed to specifically assess any potential interactions between ART and HRT preparations containing oestradiol. There are concerns that there may be drug–drug interactions between HRT and boosted protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) except rilpivirine because of their effects on the cytochrome P450 (CYP) pathways, shared by reproductive hormones. It may therefore be necessary to titrate hormone levels to achieve the desired therapeutic effect or limit toxicity. In our study, estrogen was up titrated in 16/28 (58%) in the HIV patients to obtain satisfactory symptom control. This may be related to low serum oestradiol levels but potentially may also have been contributed to by drug–drug interactions. ART drugs such as integrase inhibitors may be substituted for PIs and rilpivirine for other NNRTIs to overcome potential drug–drug interactions in WLHIV who wish to consider HRT.[18,19]

One study by Samselle et al. found that cultural differences in attitudes to the menopause meant that Caucasian women were more concerned with the symptoms of the menopause, whereas African women viewed it as normal or even welcomed it.[20]

It is clear that this subgroup of women is at risk of menopause-related co-morbidities. However, it appears that a significant proportion of WLHIV are not receiving hormonal replacement either due to a reluctance to start HRT or through discontinuation as demonstrated by our study findings and other recent reports. These findings need to be further evaluated in larger studies to explore the underlying reasons behind this. In addition, there is a need to further evaluate the cultural differences in perception of the menopause, its related symptoms and the uptake of HRT. There is also a need to increase awareness regarding the role and benefits of HRT in WLHIV both in the context improving well-being as well as menopausal symptom management and quality of life.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: HH has acted in an advisory capacity for Bayer.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: HH has received a research grant to support a clinical trial and support to attend academic conferences from Besins.

Guarantor

HH.

Contributorship

HH, MS and CT conceived the study. MS, CT and HH undertook the clinics where the data were retrieved from. PH and MM analysed the data. PH, MM, MS and HH wrote the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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