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Do women with HIV/AIDS on anti-retroviral therapy have a lower incidence of symptoms associated with menstrual dysfunction?

Nicola Tempest [a,b,*], Damitha N Edirisinghe [c], Steven Lane [d], Dharani K Hapangama [a,b]

[a] Liverpool Women's Hospital NHS Foundation Trust, Member of Liverpool Health Partners, Liverpool L8 7SS, UK
[b] Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool, Member of Liverpool Health Partners, Liverpool L8 7SS, UK
[c] Axess Sexual Health Liverpool, Liverpool University Hospitals NHS Foundation Trust, Member of Liverpool Health Partners, Liverpool L7 8XP, UK
[d] Department of Biostatistics, Institute of Life Course and Medical Sciences, University of Liverpool, Member of Liverpool Health Partners, University of Liverpool, Liverpool L69 3BX, UK

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ABSTRACT

Background: Symptoms associated with menstruation and endometriosis are common amongst women of reproductive ages and the pathogenesis of these illnesses is postulated to be associated with aberrations in endometrial regeneration, immune response and in endometrial stem cell function. Highly active antiretroviral therapy (HAART) has been shown to enhance events seen in biological aging of tissues, with HIV/AIDS patients enduring the premature appearance of illnesses associated with stem-cell aging. Considering the intricate relationship between dysregulation of stem cell function, in both HAART therapy and in menstrual disorders/endometriosis, we sought to examine the prevalence of menstrual related symptoms (MRS) associated with endometriosis in women on HIV/AIDS therapy.

Methods: A menstrual related symptoms (MRS) questionnaire adapted from the British Society of Gynaecological Endoscopists (BSGE) pelvic pain questionnaire, which has been used in both clinical and research setting, was completed by 100 women living with HIV (WLWH) attending a specialist HIV clinic and by 100 women without a diagnosis of HIV attending the Sexual Health clinic (WWH). HIV related demographic details, including results from recent blood tests, were also recorded prospectively from the WLWH.

Results: WLWH were slightly older (37.7 vs. 34.8 years, P = 0.01); with higher BMI (28.9 vs. 24.8, P < 0.001); and were likely to be parous (85% vs. 54% P < 0.001) and non-Caucasian (79% vs 18%) compared with WWH. Most women in both groups had regular periods (77.9% vs. 74.7%), and WLWH were more likely to have a shorter duration of bleeding compared with WWH (81.4% vs 69.3% P = 0.05). However, WLWH were more likely to suffer with pre-menstrual tension compared with WWH (60.8% vs 50.6% P = 0.01).

Conclusion: Our data suggests that WLWH, despite being older and of higher BMI, have a shorter duration of menstrual bleeding, and we hypothesise that this may possibly be due to the (beneficial) side effects of some HAART components. Further research is needed to explore the effect of HAART on MRS to determine if these therapies could be used in the future as a fertility retaining treatment for MRSs/endometriosis.

Background

Menstruation related symptoms (MRS) including heavy menstrual bleeding, dysmenorrhoea and premenstrual mood disturbances are common causes of absenteeism in young females [1], linked to nearly nine days of lost productivity every year through presenteeism [2–4]. For example, up to one in three premenopausal women experience heavy menstrual bleeding [5]. Studies show that women with MRSs have lower scores on several domains of quality of life such as general health and physical, mental, social and occupational functioning during their periods

Abbreviations: AIDS, acquired immune deficiency syndrome; BSGE, British society of gynaecological endoscopists; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MRSs, menstruation related symptoms; NRTIs, nucleoside reverse transcriptase inhibitors; WLWH, women living with HIV; WWH, women without HIV.

* Corresponding author at: Department of Women's and Children's Health, Institute of Translational Medicine, University of Liverpool, Liverpool L8 7SS, United Kingdom.

E-mail address: Ntempest@liverpool.ac.uk (N. Tempest).

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[2,4,6,7]. With lost productivity, considerable financial burdens could be placed on families as well as on society in general [2]. Unfortunately, many currently available gynaecological treatment options (excluding analgesia) are based on agonists or antagonists of steroid hormone receptors, thus are associated with hormonal side effects, and are contraceptive. Their lack of efficacy leads to frequent discontinuation and many women progress to resolute in high risk surgical interventions [8].

Endometriosis is a common, chronic gynaecological condition defined by the presence of extrauterine, yet oestrogen responsive endometrial tissue [9]. At least 1 in 10 women of reproductive age in the UK suffer from endometriosis, which is responsible for significant morbidity and places a huge economic burden on the women, health services and society [10]. Although the incidence is similar to other chronic conditions such as asthma, the treatment options for endometriosis associated symptoms such as MRSs remain limited, with no effective, novel, non-hormonal treatment options introduced to routine clinical practice for several decades. This is of particular importance since routine hormonal treatment or repeated surgery is not suitable for women who are seeking conception, and thus at present, millions of young women have to suffer MRSs, pre-conceptionally every year.

Highly active antiretroviral therapy (HAART) has been shown to enhance events seen in biological aging of tissues, and illnesses associated with stem-cell aging, appear prematurely in human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) patients [11]. The specific component of HAART relevant to features resembling ageing are thought to be nucleoside reverse transcriptase inhibitors (NRTIs) due to their off-target anti-telomerase activity [11,12]. The safety record of these treatments are well-established and they are licenced to be used in pregnancy and in healthy people as pre/post exposure prophylactic therapy.

The pathophysiology of MRSs and endometriosis is hypothesised to be due to abnormalities in endometrial regeneration, immune response, telomerase and in endometrial stem cell function. High telomerase activity is a feature of endometrial epithelial progenitor cells [13] and in the endometrium of patients with endometriosis [14]. Progesterone is a common treatment for both MRSs and endometriosis, and it decreases endometrial telomerase activity *in vivo* and *in vitro* [15]. The incidence of MRSs in women on NRTIs is not well established, with reported studies confounded by HIV/AIDs associated clinical features in participants that may also affect MRSs. In developed countries, including the UK, HIV positive women have their viral load kept to a minimum with HAART, this commonly includes NRTIs, thus their survival and life expectancy is comparable to that of their counterparts, without a diagnosis of HIV [16,17]. Very little is known of the prevalence of MRS in WLWH, with no published data on the frequency of diagnosis or of the symptoms associated with endometriosis in this population in the literature. Our objective therefore was to fill this gap in current literature and assess the prevalence of MRSs and symptoms associated with endometriosis in WLWH and in a population of women without a diagnosis of HIV (WWH), attending an NHS sexual health clinic in England.

Materials and methods

This questionnaire study was approved by North West - Liverpool Central Research Ethics Committee (14/NW/1289).

Axess Sexual Health is the largest provider of HIV care in Cheshire and Merseyside, with a specialist tertiary level HIV clinic, which sees approximately 1300 patients a year. A total of 100 WLWH accepted the verbal invitation, conferred informed consent and completed the questionnaire during their routine clinic attendance. A further group of 100 women, without a diagnosis of HIV (WWH) attending the Axess Sexual Health clinic were also recruited to complete the questionnaire. The WLWH were given information regarding the study on arrival at their routine clinical appointment, if they were happy to participate, they signed a written informed consent form, completed a questionnaire (Supplementary figure I) and the attending doctor recorded the patient's HIV related history including results of their recent blood tests confirming the disease status. The WWH also received information with an accompanying questionnaire on their arrival to clinic and if they chose to take part, they voluntarily completed the questionnaire, which was returned to the box provided. No personal identifiers were collected from the WWH and the patient information sheet clearly described that consent was assumed if they voluntarily returned the questionnaire. The questionnaire included themes of basic non-person identifying demographic information; such as age, height, weight and parity and multiple choice-questions about menstruation length, regularity and various types of associated pain from the British Society of Gynaecological endoscopy (BSGE) pelvic pain questionnaire[18]. This questionnaire had been used routinely in clinical practice in the UK, in all BSGE accredited endometriosis clinics and also had been used in research settings [18].

The responses to these questionnaires were uploaded on to an excel spreadsheet before being migrated into SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) and analysed using independent sample *t*-test, Mann-Whitney *U* test and Chi-squared tests as appropriate.

Results

Demographic information of the study population

The two groups of women differed in the following demographic features; WLWH were slightly older (37.7 vs 34.8 years, P = 0.01), they had a higher BMI (28.9 vs 24.8, P < 0.001); they were more likely to be of non-Caucasian ethnicity (79% vs 18%) and most women in this group were parous (85% vs 54% P < 0.001) (Table 1). Subgroup analysis demonstrated demographic differences between the groups (Tables 2 and 3) to continue, excluding age, in the women not on hormonal contraceptive treatment (Table 2).

A similar proportion of women in both groups did not use contraceptives (30% vs 29%) and as expected, more WLWH used condoms (41% vs 22%) as their contraceptive method (Table 1). This higher use of condoms persisted even within the subgroup analysis, when the use or non-use of hormonal contraceptives were considered (Table 2 and 3). The Mirena Intra Uterine System was the second most popular method of contraception (11% vs 16%) (Table 1). When the subgroup of women who were taking hormonal medications were considered, the types of hormonal contraception utilised in the two groups were very different (Table 3). The WLWH mainly used progesterone containing contraception (95%) but conversely, the WWH included a large number of women on the combined oral contraceptive pill (COCP) (oestrogen and progesterone) (34.1%) (Table 3).

The WLWH were more likely to take other medications, excluding HAART (41% vs 23.2% P = 0.008) and regardless of being on hormonal contraceptives or not (Tables 1, 2 and 3).

HIV status of WLWH;

The mean duration since HIV diagnosis in our study cohort was 8.41 years and only 4 patients had been diagnosed with AIDs. Most had a CD4 count of > 400 (82%), a low viral load of < 50 (93%) and a median duration of HAART of 6 years (Supplementary table 1). The

Table 1
Demographics of all women in the study.

Variable	WLWH (n = 100)	WWH (n = 100)	Significance
Age mean (st. dev.)	37.7 (7.82)	34.8 (8.23)	P = 0.01[1]
BMI mean (st. dev)	28.9 (7.87)	24.8 (5.41)	P < 0.001[1]
Nulliparity n (%)	15 (15)	46 (46)	P < 0.001[2]
Ethicity White	21 (21)	82 (82)	NA
n (%) Black African	68 (68)	2 (2)	
Black Caribbean	2 (2)	1 (1)	
Asian	2 (2)	8 (8)	
Other	7 (7)	7 (7)	
Contraception Condoms	41 (41)	22 (22)	NA
n (%) POP	1 (1)	4 (4)	
COCP	1 (1)	14 (14)	
Mirena	11 (11)	16 (16)	
CuCoil	3 (3)	3 (3)	
Depo	5 (5)		
Sterilised	6 (6)	3 (3)	
Progesterone implant	2 (2)	7 (7)	
Other		2 (2)29	
No contraception	30(30)	(29)	
Past medical history other than HIV			
n (%) Yes	46 (46.0)54	35 (35.8)61	P = 0.15[3]
No	(54.0)	(64.2)	
Medication other than HAART			
n (%) Yes	41 (41.0)59	22 (23.2)73	P = 0.008[3]
No	(59.0)	(76.8)	

WLWH (women living with HIV), WWH (women without HIV), POP (progesterone only pill), COCP (combined oral contraceptive pill), CuCoil (copper coil), Depo (Depo-provera), HAART (highly active anti-retroviral treatment).
[1] Independent sample *t*-test [2] Chi-squared test [3] Mann-Whitney *U* test.

Table 2
Demographics of the women not on hormonal contraceptive treatment.

Variable	WLWH (n = 80)	WWH (n = 59)	Significance
Age mean (st. dev.)	37.5 (7.96)	36.1 (8.39)	P = 0.29[1]
BMI mean (st. dev)	28.6 (6.86)	24.6 (5.11)	P < 0.001[1]
Nulliparity n (%)	14 (17.5)	22 (37.3)	P = 0.008[2]
Ethicity White	18 (22.5)53	45 (76.3)	NA
n (%) Black African	(66.2)2	1	
Black Caribbean	(2.5)2	(1.7)7	
Asian	(2.5)5	(11.9)6	
Other	(6.3)	(10.1)	
Contraception Condoms	41 (51.2)3	22 (37.3)3	NA
n (%) CuCoil	(3.8)6	(5.1)3	
Sterilised	(7.5)	(5.1)2	
Other	30	(3.4)29	
No contraception	(37.5)	(49.1)	
Past medical history other than HIV	36 (45.0)44	20 (36.4)35	P = 0.32[3]
n (%) Yes	(55.0)	(63.3)	
No			
Medication other than HAART	33	12	
n (%) Yes	(41.3)47	(21.8)43	P = 0.02[3]
No	(58.8)	(78.2)	

WLWH (women living with HIV), WWH (women without HIV), POP (progesterone only pill), COCP (combined oral contraceptive pill), CuCoil (copper coil), Depo (Depo-provera), HAART (highly active anti-retroviral treatment).
[1] Independent sample *t*-test [2] Chi-squared test [3] Mann-Whitney *U* test.

most common anti-retroviral therapy used was a combination of Truvada (NRTI), Darunavir (protease inhibitor) and Ritonavir (used as a booster for Darunavir).

Table 3
Demographics of the women on hormonal contraceptive treatment.

Variable	WLWH (n = 20)	WWH (n = 41)	Significance
Age Mean (st. dev.)	38.3 (7.44)	33.1 (7.77)	P = 0.02[1]
BMI Mean (st. dev)	30.3 (10.88)	25.1 (5.57)	P = 0.02[1]
Nulliparity n (%)	1 (5.0)	24 (58.5)	P < 0.001[2]
Ethicity White	3 (15.0)15	37 (90.3)2	NA
n (%) Black African	(75.0)	(4.9)	
Black Caribbean		1	
Asian	2	(2.4)1	
Other	(10.0)	(2.4)	
Contraception POP	1 (5.0)1	4 (9.8)14	NA
n (%) COCP	(5.0)11	(34.1)16	
Mirena	(55.0)5	(39.0)	
Depo	(25.0)2	7	
Progesterone implant	(10.0)	(17.1)	
Past medical history other than HIV	10 (50.0)10	14 (35.0)26	P = 0.26[3]
n (%) Yes	(50.0)	(65.0)	
No			
Medication other than HAART	8	10	
n (%) Yes	(40.0)12	(25.0)30	P = 0.23[3]
No	(60.0)	(75.0)	

WLWH (women living with HIV), WWH (women without HIV), POP (progesterone only pill), COCP (combined oral contraceptive pill), CuCoil (copper coil), Depo (Depo-provera), HAART (highly active anti-retroviral treatment).
[1] Independent sample *t*-test [2] Chi-squared test [3] Mann-Whitney *U* test.

Incidence of MRSs

Regularity of menstrual bleeding;

The majority of women in both groups reported regular menstrual bleeding (77.9% vs 74.7%) (Table 4). The duration of menstrual bleeding $\geq$ 6 days was lower in the WLWH (18.6% vs 30.7% P = 0.05). This observation remained to be constant even when the subgroup of women not on hormonal preparations were considered P = 0.03 (Table 5), but excluding the subgroup of women on hormonal preparations (P = 0.48) (Table 6).

Heavy menstrual bleeding

No significant differences were noted with heavy menstrual bleeding across all groups and subgroups of women

Premenstrual tension

Pre-menstrual tension was a more frequent complaint in the WLWH (60.8% vs 50.6% P = 0.01) (Table 4) when all women were analysed together, this difference was also apparent in the subgroup of women on hormones (P = 0.05) (Table 6), but not when the women were not on hormones (Table 5).

Dysmenorrhoea and non-cyclical pelvic pain

No statistically significant rates of dysmenorrhoea were noted between both groups of women (Table 4) and between the subgroup of women who were not on hormones (Table 5). However, when those on hormonal preparations were considered separately, WLWH had a significantly higher incidence of dysmenorrhoea than those WWH (62% vs 19% P = 0.01) (Table 6), perhaps due to the differing hormonal preparations used. Symptoms of non-cyclical pelvic pain and dyspareunia did not show any significant differences between the two groups.

Access to gynaecology consultation

In general, the majority of women in both groups had never seen a doctor about their MRSs (63.9% study group vs 65.3% control group), with less WLWH reported to have consulted a gynaecolo-

Table 4
Questionnaire results of all women in the study.

Variable	WLWH (n = 100)	WWH (n = 100)	Significance
Regular periods n (%)	74 (77.9)	68 (74.7)	P = 0.61[2]
Length of periods No period	5 (5.5)28	12 (12.9)24	NA
n (%) < 28 days	(30.8)39	(25.8)	
28 Days	(42.8)19	27	
>28 days	(20.9)	(29)30	
		(32.3)	
Duration of bleeding 1–2 days	1 (1.1)53	4 (4.7)27	NA
n (%) 3–4 days	(55.8)32	(31.45)38	
5–6 days	(33.7)7	(44.2)13	
7–8 days	(7.4)2	(15.1)4	
9 + days	(2.1)	(4.7)	
Duration of bleeding ≤ 5 days	78 (82.1)17	60 (69.8)26	P = 0.05[2]
n (%) ≥ 6 days	(17.9)	(30.2)	
HMB Yes	41 (44.1)52	38 (42.2)52	P = 0.75[2]
n (%) No	(55.9)	(57.8)	
PMT Yes	45 (60.8)29	44 (50.6)33	P = 0.01[2]
n (%) No	(39.2)	(37.9)10	
NA		(11.5)	
Dysmenorrhoea VAS 1	1 (2.2)0	2 (3.0)13	NA
n (%) 2	(0)5	(19.4)10	
3	(10.9)5	(14.9)8	
4	(10.9)6	(11.9)2	
5	(13.0)8	(3.0)11	
6	(17.4)7	(16.4)9	
7	(15.2)4	(13.4)6	
8	(8.7)6	(9.0)4	
9	(13.8)4	(6.0)2	
10	(8.7)	(3.0)	
Dysmenorrhoea VAS ≥ 7 n (%)	21 (45.7)	21 (31.3)	P = 0.99[2]
Non-cyclical pelvic pain	22 (29.7)52	19 (22.6)63	P = 0.27[2]
Yes n (%) No	(70.3)	(75.0)2	
NA		(2.4)	
Dyspareunia Yes	14 (18.7)57	13 (15.1)68	P = 0.83[3]
n (%) No	(76.0)4	(79.1)5	
NA	(5.3)	(5.8)	
Medical help regarding periods	62	62	
n (%) No	(63.9)19	(65.3)13	NA
Yes GP	(19.6)16	(13.7)20	
Yes gynaecologist	(16.5)	(21)	

WLWH (women living with HIV), WWH (women without HIV), HMB (heavy menstrual bleeding), PMT (premenstrual tension).
[1]Independent sample *t*-test [2]Chi-squared test [3]Mann-Whitney *U* test.

Table 5
Questionnaire results of the women not on hormonal contraceptive treatment.

Variable	WLWH n = 80	WWH n = 59	Significance
Regular periods n (%)	68 (86.1)	50 (84.7)	P = 0.83[2]
Length of periods No period	1 (1.4)22	1 (1.8)19	NA
n (%) < 28 days	(29.7)37	(34.5)15	
28 Days	(50.0)14	(27.3)20	
>28 days	(18.9)	(36.4)	
Duration of bleeding 1–2 days	1 (1.25)45	3 (5.5)20	NA
n (%) 3–4 days	(56.25)27	(36.4)22	
5–6 days	(33.8)6	(40.0)10	
7–8 days	(7.5)1	(18.2)0	
9 + days	(1.25)	(0)	
Duration of bleeding ≤ 5 days	70 (87.5)	40 (72.7)	P = 0.03[2]
n (%) ≥ 6 days	10 (12.5)	15 (27.3)	
HMB Yes	35 (45.5)	30 (50.8)29	P = 0.67[2]
n (%) No	42	(49.2)	
	(54.5)		
PMT Yes	34 (57.6)	29 (55.8)	P = 0.84[2]
n (%) No	25	23	
	(42.4)	(44.2)	
Dysmenorrhoea VAS 1	0 (0)0	2 (4.3)6	NA
n (%) 2	(0)3	(13.0)7	
3	(9.1)5	(15.2)5	
4	(15.2)5	(10.9)1	
5	(15.2)7	(2.2)8	
6	(21.2)3	(17.4)7	
7	(9.1)2	(15.2)6	
8	(6.1)5	(13.0)2	
9	(15.2)3	(4.3)2	
10	(9.1)	(4.3)	
Dysmenorrhoea VAS ≥ 7 n (%)	13 (39.4)	17 (30.9)	P = 0.68[2]
Non-cyclical pain Yes	19 (32.2)	12 (23.1)	P = 0.29[2]
n (%) No	40	40	
	(67.8)	(76.9)	
Dyspareunia Yes	12 (20.0)45	5 (9.8)43	P = 0.33[3]
n (%) No	(75.0)3	(84.3)3	
NA	(5.0)	(5.9)	
Medical help regarding periods No	54 (70.1)	40 (72.7)3	NA
n (%) Yes GP	15	(5.5)12	
Yes gynaecologist	(19.5)8	(21.8)	
	(10.4)		

[1] Independent sample *t*-test [2] Chi-squared test [3] Mann-Whitney *U* test.
WLWH (women living with HIV), WWH (women without HIV), HMB (heavy menstrual bleeding), PMT (premenstrual tension).

gist (16.5% vs 21%) (Table 4). This trend persisted when the subgroup of women not on hormones were analysed, and less WLWH consulted a gynaecologist (10.4 vs 21.8%) (Table 5) however, this observation was reversed in the subgroup of women on hormones, where 40% of those WLWH had consulted a gynaecologist and only 20% of WWH had done the same (Table 6). Only three women in total documented that they had previously been diagnosed with gynaecological conditions, all three had seen a gynaecologist and were on hormonal treatments; one WLWH had fibroids, one WWH had polycystic ovarian syndrome and a further WWH had both polycystic ovarian syndrome and endometriosis.

Discussion

This manuscript describes the MRS in a well-defined group of WLWH and WWH in a high-income setting (UK). We have identified that our entire cohort of WLWH and the subgroup of WLWH who are not on hormonal medications, have a shorter duration of menstrual bleeding compared to their counterparts without a diagnosis of HIV. They however complained of premenstrual tension more frequently than the WWH.

NRTIs have an off-target anti-telomerase effect and high telomerase is associated with endometrial proliferative disorders [15,19]. We therefore hypothesise the beneficial effect on the length of bleeding we identify may be secondary to this anti-telomerase activity. NRTIs have the unique advantage over existing treatments in allowing patients to retain their fertility, thus, this potential (beneficial) side effect of NRTIs may warrant further examination, as a non-hormonal treatment for prolonged menstrual bleeding.

According to previous publications, the reported prevalence of MRSs in WLWH have a wide variation. For example, in a large Nigerian cohort (n = 2549), MRSs were significantly more common in WLWH/AIDS compared with the HIV-negative women (29.1% vs 18.9% P < 0.001) [20]. However, that cohort differs quite significantly from our cohort of women in the UK. Several confounders were identified in the Nigerian cohort, and CD4 < 200 (odds ratio [OR], 3.65; 95% confidence interval [CI], 1.2–9.7), BMI < 20 (OR, 2.4; 95%CI, 1.3–3.5) and not taking antiretroviral drugs (OR, 2.05; CI, 1.7–6.5) were associated with amenorrhoea, oligomenorrhoea, irregular periods and secondary dysmenorrhoea [20]. A systematic review including 6570 WLWH, had concluded that WLWH have significantly high rates of amenorrhoea, but in the majority of the included studies, amenorrhea in the setting of low BMI was

Table 6
Questionnaire results of the women on hormonal contraceptive treatment.

Variable	WLWH (n = 20)	WWH (n = 41)	Significance
Regular periods n (%)	6 (30)	18 (43.9)	0.23[2]
Length of periods No period n (%) < 28 days 28 days >28 days	4 (23.5)6 (35.3)2 (11.8)5 (29.4)	11 (28.9)5 (13.2)12 (31.6)10 (26.3)	NA
Duration of bleeding 1–2 days n (%) 3–4 days 5–6 days 7–8 days 9 + days	0 (0)5 (33.3)8 (53.3)1 (6.7)1 (6.7)	1 (3.2)11 (35.5)14 (45.2)4 (12.9)1 (3.2)	NA
Duration of bleeding ≤ 5 days n (%) ≥ 6 days	8 (53.3) 7 (46.7)	20 (63.6) 11 (36.4)	0.48[2]
HMB Yes n (%) No	6 (37.5)10 (62.5)	8 (25.8)23 (74.2)	0.42[2]
PMT Yes n (%) No NA	11 (73.3)4 (26.7)	15 (42.9)10 (28.6)10 (28.6)	P = 0.05[2]
Dysmenorrhoea VAS 1 n (%) 2 3 4 5 6 7 8 9 10	1 (7.7)0 (0)2 (15.4)0 (0)1 (7.7)1 (7.7)4 (30.8)2 (15.4)1 (7.7)1 (7.7)	0 (0)7 (33.3)3 (14.3)3 (14.3)1 (4.8)3 (14.3)2 (9.5)0 (0)2 (9.5)0 (0)	NA
Dysmenorrhoea VAS ≥ 7 n (%)	8 (61.5)	4 (19.0)	P = 0.01[2]
Non-cyclical pelvic pain Yes n (%) No NA	3 (20.0)12 (80.0)	7 (21.9)23 (71.9)2 (6.2)	P = 0.59[2]
Dyspareunia Yes n (%) No NA	2 (13.3)12 (80.0)1 (6.7)	8 (22.9)25 (71.4)2 (5.7)	P = 0.74[3]
Medical help regarding periods No n (%) Yes GP Yes gynaecologist	8 (40)4 (20)8 (40)	22 (55)10 (25)8 (20)	NA

WLWH (women living with HIV), WWH (women without HIV), HMB (heavy menstrual bleeding), PMT (premenstrual tension).
[1] Independent sample *t*-test [2] Chi-squared test [3] Mann-Whitney *U* test.

significantly more frequent in WLWH than controls [21]. In contrast to those studies, the WLWH in our cohort were nearly all on HAART, had a CD4 count of > 400 and had higher BMIs than the WWH, thus we believe the reported MRSs in the Nigerian study to be related to these AIDs-associated clinical features.

Agreeing with our findings, a multicentre prospective cohort study examining the natural history of HIV in America, reported that both the use of HAART and resulting higher CD4 counts were linked to a lower incidence of MRSs in WLWH [22]. However, only 16% of the American cohort commenced HAART [22] therefore the populations are not comparable. A further American cross-sectional survey reported a 32% incidence of MRS in 107 Caucasian WLWH, but these symptoms were significantly more frequent in those with a detectable viral load, and the menstrual disorders were associated with poor adherence to HAART [23].

A large Canadian cross-sectional questionnaire study reported over half of the WLWH (not taking any hormonal contraceptives) to have abnormal menstruation [24]. The authors defined the presence or absence of abnormal menstruation, based on the responses to five questions about menstrual regularity, frequency, volume, duration, and intermenstrual bleeding. Further interrogation of their findings, demonstrates prolonged menstrual bleeding, which they defined as bleeding >7 days affected only 3.9% of women [24]. Although that particular manuscript concluded that the use of HAART correlated with MRSs and that hormonal contraceptive treatment should be preferentially offered to WLWH, their conclusions need to be re-considered for the following reasons. They did not assess the incidence of abnormal menstruation in WWH, therefore, the assumption that these symptoms are more frequent in WLWH is not justified; furthermore, our data suggested that WLWH who were on hormonal treatments to be suffering with more MRSs symptoms than both the WWH on hormones as well as WLWH who were not on hormones. Our data thus encourage future studies to examine if there are particular hormonal preparations that are associated with altering the menstrual bleeding pattern in WLWH.

Due to potential interactions with some HAART medications, combined oral contraceptive pills are not commonly used in WLWH, and irregular bleeding pattern is more common with progestogen only contraceptives in comparison with combined oral contraceptive pills, this may explain some of our observed results.

Information on MRSs (apart from that related to HIV status; e.g. diagnosis and blood parameters) collected in this anonymous, voluntary self-completed questionnaire study was not confirmed directly using medical records. However, our questionnaire, involving WLWH in a UK setting with free access to HAART and a high level of medical care including a comparable group of WWH, allowed us to assess the possible alterations in clinically relevant gynecological symptoms. In this context, with universal access to free medical care, many women, both WLWH and WWH despite suffering with MRS, still had not consulted a gynaecologist. WLWH were even less likely to have consulted a gynaecologist, compared with WWH despite being older with a higher BMI than the WWH and of non-Caucasian ethnicity [25–27]. Future studies are needed to assess the reasons for this suggested obstacle to gynaecology services and to explore if there are any specific benefits of HAART or interactions between HAART and the common contraceptive methods used in the UK.

Conclusion

Our data suggests that WLWH in the UK have decreased duration of menstrual bleeding, and we hypothesise that this may possibly be due to the (beneficial) side effects of some HAART components (e.g. NRTIs on endometrial telomerase activity). WLWH are living longer and healthier lives with improved treatment HAART regimen, and further research is needed to explore the effect of HAART on MRSs in these women to further improve their quality of life. The potential beneficial side effects of NRTIs on MRSs needs to be explored in order to determine if they could be utilised to treat MRSs/endometriosis whilst allowing women to retain fertility.

Declarations

Ethics approval and consent to participate

This questionnaire study was approved by North West - Liverpool Central Research Ethics Committee (14/NW/1289). Written informed consent was obtained for the participants with HIV and inferred informed consent was utilised when the women without HIV completed questionnaires. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

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Author contributions

DKH conceived the study, and obtained ethical approval with NT. DE and NT collected data and SL, NT and DKH analysed the data. NT and DKH interpreted the data and wrote the first draft of the manuscript. All authors revised the manuscript critically for important intellectual content and approved the submitted final version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejogrb.2021.08.027.

References

[1] Rafique N, Al-Sheikh MH. Prevalence of menstrual problems and their association with psychological stress in young female students studying health sciences. Saudi Med J 2018;39(1):67–73.
[2] Schoep ME, Adang EMM, Maas JWM, De Bie B, Aarts JWM, Nieboer TE. Productivity loss due to menstruation-related symptoms: a nationwide cross-sectional survey among 32 748 women. BMJ Open. 2019;9(6):e026186. https://doi.org/10.1136/bmjopen-2018-026186.
[3] Growing. Learning. Extracting.
[4] Munro MG, Critchley HOD, Fraser IS, Committee FMD. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet 2018;143(3):393–408.
[5] RCOG. National heavy menstrual bleeding audit. 2014.
[6] Hapangama DK, Bulmer JN. Pathophysiology of heavy menstrual bleeding. Womens Health (Lond). 2016;12(1):3–13.
[7] Excellence NIfHaC. Heavy menstrual bleeding: assessment and management. Nice Guideline 88 2018;Updated March 2020.
[8] Maybin JA, Critchley HOD. Medical management of heavy menstrual bleeding. Womens Health (Lond). 2016;12(1):27–34.
[9] Sourial S, Tempest N, Hapangama DK. Theories on the pathogenesis of endometriosis. Int J Reprod Med. 2014;2014:1–9.
[10] Tempest N, Maclean A, Hapangama D. Endometrial stem cell markers: current concepts and unresolved questions. Int J Mol Sci 2018;19(10):3240. https://doi.org/10.3390/ijms19103240.
[11] Leeansyah E, Cameron PU, Solomon A, Tennakoon S, Velayudham P, Gouillou M, et al. Inhibition of telomerase activity by human immunodeficiency virus (HIV) nucleos(t)ide reverse transcriptase inhibitors: a potential factor contributing to HIV-associated accelerated aging. J Infect Dis. 2013;207(7):1157-65.
[12] Hukezalie KR, Thumati NR, Côté HCF, Wong JMY, Sluis-Cremer N. In vitro and ex vivo inhibition of human telomerase by anti-HIV nucleoside reverse transcriptase inhibitors (NRTIs) but not by non-NRTIs. PLoS ONE 2012;7(11):e47505.
[13] Valentijn AJ, Palial K, Al-Lamee H, Tempest N, Drury J, Von Zglinicki T, et al. SSEA-1 isolates human endometrial basal glandular epithelial cells: phenotypic and functional characterization and implications in the pathogenesis of endometriosis. Hum Reprod. 2013;28(10):2695-708.
[14] Hapangama DK, Turner MA, Drury JA, Quenby S, Saretzki G, Martin-Ruiz C, et al. Endometriosis is associated with aberrant endometrial expression of telomerase and increased telomere length. Hum Reprod 2008;23(7):1511–9.
[15] Hapangama DK, Kamal A, Saretzki G. Implications of telomeres and telomerase in endometrial pathology. Hum Reprod Update. 2017;23(2):166–87.
[16] Lohse N, Obel N. Update of Survival for Persons With HIV Infection in Denmark. Ann Intern Med 2016;165(10):749–50.
[17] Andany N, Kennedy VL, Aden M, Loutfy M. Perspectives on menopause and women with HIV. Int J Womens Health. 2016;8:1–22.
[18] Byrne D, Curnow T, Smith P, Cutner A, Saridogan E, Clark TJ. Laparoscopic excision of deep rectovaginal endometriosis in BSGE endometriosis centres: a multicentre prospective cohort study. BMJ Open. 2018;8(4):e018924. https://doi.org/10.1136/bmjopen-2017-01892410.1136/bmjopen-2017-018924.supp110.1136/bmjopen-2017-018924.supp2.
[19] Valentijn AJ, Saretzki G, Tempest N, Critchley HO, Hapangama DK. Human endometrial epithelial telomerase is important for epithelial proliferation and glandular formation with potential implications in endometriosis. Hum Reprod 2015;30(12):2816–28.
[20] O.C. Ezechi A. Jogo C. Gab-Okafor D.I. Onwujekwe P.M. Ezeobi T. Gbajabiamila et al. Effect of HIV-1 infection and increasing immunosuppression on menstrual function 36 5 2010 1053 1058
[21] King EM, Albert AY, Murray MCM. HIV and amenorrhea: a meta-analysis. AIDS. 2019;33(3):483–91.
[22] Massad LS, Evans CT, Minkoff H, Watts DH, Greenblatt RM, Levine AM, et al. Effects of HIV infection and its treatment on self-reported menstrual abnormalities in women. J Womens Health (Larchmt). 2006;15(5):591–8.
[23] Fumaz CR, Muñoz-Moreno JA, Ferrer MJ, Negredo E, Pérez-Álvarez N, Tarrats A, et al. Low levels of adherence to antiretroviral therapy in HIV-1-infected women with menstrual disorders. AIDS Patient Care STDS. 2009;23(6):463–8.
[24] Valiaveettil C, Loutfy M, Kennedy VL, Caddy S, Yudin M, Conway T, et al. High prevalence of abnormal menstruation among women living with HIV in Canada. PLoS ONE 2019;14(12):e0226992.
[25] Marsh EE, Ekpo GE, Cardozo ER, Brocks M, Dune T, Cohen LS. Racial differences in fibroid prevalence and ultrasound findings in asymptomatic young women (18–30 years old): a pilot study. Fertil Steril 2013;99(7):1951–7.
[26] Ko KM, Han K, Chung YJ, Yoon KH, Park YG, Lee SH. Association between body weight changes and menstrual irregularity: The Korea national health and nutrition examination survey 2010 to 2012. Endocrinol Metab (Seoul) 2017;32(2):248–56.
[27] Kafaei-Atrian M, Mohebbi-Dehnavi Z, Sayadi L, Asghari-Jafarabadi M, Karimian-Taheri Z, Afshar M. The relationship between the duration of menstrual bleeding and obesity-related anthropometric indices in students. J Educ Health Promot 2019;8:81.