Factors associated with early menopause among women in Nigeria

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Abstract

Objectives: Effective antiretroviral therapy has prolonged the survival of patients with HIV. Accordingly, studies of the consequences of ageing are increasingly important. We determined the prevalence of early menopause (EM) and its associated factors in a cohort of HIV-infected and HIV-negative controls in Jos, Nigeria.

Methods: HIV-infected women accessing care in an ambulatory setting and their negative counterparts from the general population were included. Menopause was defined as having gone one year since the last menstrual period. EM was defined as the onset of menopause at ≤45 years of age. Baseline characteristics were compared and logistic regression analyses were used to determine factors independently associated with EM.

Results: Out of a total of 253 women included, 58 attained menopause early, giving an EM prevalence of 22.9% (95% confidence interval [CI] 17.9–28.6%). Women with EM were younger (P<0.001) and had been infected with HIV for a shorter period (P=0.007). Baseline CD4+ cell count (P=0.66) and viral load (P=0.15) were similar among those with and without EM. For all subjects, HIV infection (adjusted odds ratio [AOR]=10.95, 95% CI 1.39–86.33) and sexual activity (AOR=2.37, 95% CI 1.24–4.52) were associated with EM while early menarche (AOR=14.88, 95% CI 1.37–161.10) and sexual activity (AOR=2.02, 95% CI 1.03–3.96) were independently associated with EM.

Conclusion: Over a quarter of our postmenopausal women attained menopause early. No HIV-related factor predicted EM in this study. A better understanding of ageing in these women is important to determine a more appropriate disease-management approach during this period of life.

Keywords: Early menopause, HIV infection, risk factors, sub-Saharan Africa

Introduction

As the HIV epidemic enters its fourth decade, a high percentage of women with HIV in sub-Saharan Africa (SSA) will be transitioning into midlife and experiencing menopause following improvement in life expectancy with the use of combination antiretroviral therapy [1,2]. Menopause has been defined as the permanent cessation of menstruation due to loss of ovarian follicular activity, clinically presenting as 12 months of amenorrhoea. The timing of natural menopause is an important risk factor for negative health outcomes [3]. Age at menopause varies substantially within and across populations, with the mean age at menopause in the developed world being typically higher than that observed in the developing world [4–6]. Data on age at menopause in women infected with HIV have been conflicting, with women living with HIV (WLHIV) tending to experience menopause at an earlier age [7,8].

Early menopause (EM) is becoming an important public health issue. It is a risk factor for infertility and has been associated with increased all-cause mortality [9–12], as well as an increased risk of other negative outcomes, such as atherosclerosis, cardiovascular disease, stroke, osteoporosis, and fracture in women from the general population [13–16]. In addition, women who experience early menopause have an increased risk of Parkinsonism, cognitive impairment or dementia, depressive and anxiety symptoms compared with women who enter naturally into the postmenopausal phase [17]. WLHIV are also at increased risk of negative cardiovascular and metabolic outcomes because of their exposure to HAART [18]. Data suggest that an earlier onset of natural menopause may be associated with HIV infection [19–21]. However, evidence of the roles of HIV-related parameters like CD4 cell count, HIV viral load and presence of AIDS-defining conditions on the risk of developing EM in WLHIV is variable, with studies reporting some or no association [7,8,20].

In the general population, socio-demographic, lifestyle, reproductive and medical [22–24] factors have been associated with early menopause, but studies on EM among WLHIV are few, especially in SSA. Given the paucity of data on reproductive ageing among women generally and HIV-infected women in particular, our objectives for this study were to determine the prevalence of EM and assess factors associated with EM amongst women in Jos, north central Nigeria.

Methods

This study is a subset analysis of women enrolled in the sexual health and quality of life study. The sexual health and quality of life study was a cross-sectional study comparing data from HIV-infected women aged 40 years and above who were receiving care at the HIV outpatient clinic of the Jos University Teaching Hospital (JUTH) and HIV-negative controls recruited from the general population. Women who met the inclusion criteria and provided written informed consent were recruited. For inclusion in the HIV-positive group, laboratory confirmation of the women’s seropositive status by Western blot was required. Women with a history of oophorectomy, nursing mothers and those too ill to participate were excluded. The clinic provides comprehensive longitudinal care to HIV-infected patients aged 15 years and above. Upon enrolment for care, patients who meet the criteria for ART initiation are commenced on non-nucleoside reverse transcriptase (NNRTI)-based highly active antiretroviral therapy (HAART), while patients not commencing HAART receive HIV care.

Women were classified premenopausal if they had regular menstrual cycles; perimenopausal if they had absence of menses in at least three cycles, but no more than 11, during the past 12 months; and postmenopausal if they had amenorrhoeic for...
12 months or more. Seven hundred and fourteen women were enrolled in the larger study. Seven were excluded because they were missing data on menstrual status. An additional 13 with history of current use of hormonal contraception were also excluded because of documented evidence of contraception-induced amenorrhoea [25–27]. Two hundred and fifty-three women had had their final menstrual period (FMP) at least 12 months prior to the time of enrolment into the study.

The following covariates were assessed using a self-administered structured questionnaire: socio-demographic (age, marital status, level of education, occupation and current employment); reproductive (age at menarche, parity, lifetime sexual partners, history of menorrhagia, history of past use of contraception and sexual activity); medical and lifestyle (history of cigarette smoking and alcohol use, self-reported history of hypertension, and diabetes mellitus). The body mass index (BMI) was calculated from weight in kilograms divided by the square of height in metres and was reported in kg/m². The following HIV-related data were retrieved from the electronic database used for patient management and monitoring [28]: hepatitis B virus (HBV) surface antigen (Monolisa HBsAg Ultra3, Bio-Rad, France), and hepatitis C virus (HCV) antibody (Dia.PRO Diagnostic, Bioprobes srl, Milan, Italy) status, and baseline World Health Organization (WHO) clinical staging. CD4 cell count, measured as cells/mm³ (Flowcytometry, Partec, Munster, Germany), and HIV viral load, measured as copies/mL (Cobas Amplicor Monitor Assay version 1.5, Roche Diagnostics, Mannheim, Germany) at entry into care (baseline) and current at the time of enrolment into the study were documented. Other variables obtained included duration of HIV infection, use of HAART and duration of use, as well as history of HAART use prior to enrolment at the JUTH HIV clinic.

Ethical considerations

This study was approved by the Human Research Ethics Committee (HREC) at the Jos University Teaching Hospital. Written informed consent was obtained from each eligible woman before participation in the study. Approval for secondary use of data was obtained from the institutional review board (IRB) at the Harvard TH Chan School of Public Health.

Data analysis

The study outcome was age at natural menopause ≤45 years, and this outcome was determined retrospectively. Natural menopause is defined by the WHO as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. This condition is clinically recognised after at least 12 months of amenorrhoea, at which time the final menstrual period (FMP) is characterised with certainty. Early natural menopause is defined as the natural onset of menopause at an age ≤45 years.

Covariates were dichotomised for multivariable analyses as follows: early menarche (age at first menstrual period <11 years); employment status (unemployed vs employed); education (none/primary vs secondary and higher); HIV status (positive vs negative); hepatitis C status (positive vs negative); duration of HIV infection and HAART use (<5 years vs ≥5 years); high baseline viral load (<100,000 copies/mL versus ≥100,000 copies/mL); baseline CD4+ cell category (≥350, 200–349, 100–199, 50–99 and 0–49 cells/mm³); and AIDS-defining illness at entry (WHO stage IV).

We used means (± standard deviation [SD]), and frequencies (%) to describe continuous and categorical variables, respectively. For non-normally distributed data, median (interquartile range [IQR]) was used. Statistical analyses for categorical variables were performed using the Chi-squared test. For continuous variables, Student’s t-test was used, and Fisher’s exact test was used when the value or count of any cell was less than 5. Associations between the dichotomised outcome variable (early menopause) and participant characteristics were examined using bivariate methods. Multivariate logistic regression models using backward elimination were used to identify factors independently associated with early menopause. The first model evaluated the total cohort (HIV-infected and uninfected subjects, n=253) and the second model included only HIV-infected subjects (n=219). Variables with P-values less than 0.20 on bivariate analysis were considered for inclusion in the final regression models. For the regression model evaluating only HIV-infected subjects, all statistically significant covariates and clinically relevant covariates (significant or not) were included in the final model. All P-values were two-tailed and significance was set at P<0.05. STATA statistical package version 13.1 (College Station, Texas, USA) was used for analyses.

Results

A total of 253 subjects were included in this analysis. The flow chart for inclusion is shown in Figure 1. The mean age of the cohort was 50±5 years and 112 (44.3%) were married. Eighty-nine (35.2%) had not received formal education and 88 (34.8%) were unemployed. Eight subjects (3.2%) reported ever having smoked cigarettes and 55 (21.7%) self-reported a history of essential hypertension. The majority (n=219, 86.6%) of the subjects were HIV positive, with a median 5 (IQR 4–7) years since HIV diagnosis. The median CD4 cell count and HIV RNA count at baseline of the participants with HIV were 216 (IQR: 138–291 cells/mm³) and 62,699 (IQR: 13,172–192,352 copies/mL), respectively, with 63 (28.8%) presenting in WHO clinical stage III/IV. Twenty-nine (13.2%) and 41 (18.7%) were co-infected with hepatitis B and C viruses, respectively and 205 (93.6%) were on HAART at the time of the study. The details of reproductive and other characteristics are shown in Table 1.

Fifty-eight of the 253 menopausal subjects were aged ≤45 years, giving an EM prevalence of 22.9% (95% CI 17.9–28.6%). When stratified by HIV status, the prevalence of EM was higher among HIV-positive compared to HIV-negative women (27.9% [95% CI 1.22–34.2%] vs 2.7% [95% CI 0.1–14.2%], P<0.001). Compared

![Figure 1. Flow chart of 253 subjects included in the study](image-url)
### Table 1. Characteristics of HIV-positive women with and without early menopause in Jos, Nigeria (n=253)

| Characteristic                          | Total=253 | Regular menopause Total=195 | Early menopause Total=58 | P-value |
|-----------------------------------------|-----------|-----------------------------|--------------------------|---------|
| **Socio-demographic**                   |           |                             |                          |         |
| Mean age, years                         | 50±5      | 52±4                        | 43±2                     | <0.001  |
| Marital status, n (%)                   |           |                             |                          |         |
| Single                                  | 3 (1.2)   | 1 (0.5)                     | 2 (3.5)                  | 0.38    |
| Married                                 | 112 (44.3)| 85 (43.6)                   | 27 (46.5)                |         |
| Widowed                                 | 119 (47.0)| 94 (48.2)                   | 25 (43.1)                |         |
| Divorced/separated                      | 16 (6.3)  | 12 (6.2)                    | 4 (6.9)                  |         |
| Missing                                 | 3 (1.2)   | 3 (1.5)                     | 0 (0.0)                  |         |
| **Educational status, n (%)**           |           |                             |                          | 0.11    |
| No formal education                     | 89 (35.2)| 65 (33.3)                   | 24 (41.4)                |         |
| Primary                                 | 60 (23.7)| 45 (23.1)                   | 15 (25.9)                |         |
| Secondary                               | 32 (12.6)| 22 (11.3)                   | 10 (17.2)                |         |
| Tertiary                                | 64 (25.3)| 55 (28.2)                   | 9 (15.5)                 |         |
| Missing                                 | 8 (3.2)   | 8 (4.1)                     | 0 (0.0)                  |         |
| **Occupation, n (%)**                   |           |                             |                          | 0.13    |
| Housewife                               | 60 (23.7)| 44 (22.6)                   | 16 (27.5)                |         |
| Civil servant                           | 100 (39.5)| 85 (43.6)                   | 15 (25.9)                |         |
| Self-employed                           | 86 (34.0)| 61 (31.3)                   | 25 (43.1)                |         |
| Missing                                 | 7 (2.8)   | 5 (2.6)                     | 2 (3.5)                  |         |
| **Current employment status, n (%)**    |           |                             |                          | 0.001   |
| Unemployed                              | 88 (34.8)| 69 (30.3)                   | 29 (50.0)                |         |
| Employed                                | 100 (39.5)| 86 (44.1)                   | 14 (24.1)                |         |
| Retired                                 | 20 (7.9) | 19 (9.7)                    | 1 (1.7)                  |         |
| Missing                                 | 45 (17.8)| 31 (15.9)                   | 14 (24.1)                |         |
| **Reproductive**                        |           |                             |                          |         |
| Mean age at menarche, years             | 15±2      | 15±2                        | 14±2                     | 0.76    |
| Early menarche (<11 years), n (%)       | 4 (1.6)   | 1 (0.5)                     | 3 (5.2)                  | 0.03    |
| Median lifetime sexual partners, n (IQR)| 1 (1–2)   | 1 (1–2)                     | 1 (1–2)                  | 0.73    |
| Sexual activity, n (%)                  |           |                             |                          | 0.11    |
| Yes                                     | 84 (33.2)| 59 (30.2)                   | 25 (43.1)                |         |
| No                                      | 163 (64.4)| 130 (66.7)                  | 33 (56.9)                |         |
| Missing                                 | 6 (2.4)   | 6 (3.1)                     | 0 (0.0)                  |         |
| Median parity, n (IQR)                  | 5 (4–7)   | 5 (4–7)                     | 5 (4–7)                  | 0.88    |
| Parity, n (%)                           |           |                             |                          | 0.68    |
| 0                                       | 8 (3.2)   | 5 (2.6)                     | 3 (5.2)                  |         |
| 1–4                                     | 93 (36.7)| 71 (36.4)                   | 22 (37.9)                |         |
| ≥5                                      | 144 (56.9)| 113 (57.9)                  | 31 (53.4)                |         |
| Missing                                 | 8 (3.2)   | 6 (3.1)                     | 2 (3.5)                  |         |
| History of menorrhagia, n (%)           |           |                             |                          | 0.96    |
| Yes                                     | 109 (43.1)| 87 (43.1)                   | 25 (43.1)                |         |
| No                                      | 132 (52.2)| 101 (51.8)                  | 31 (53.4)                |         |
| Missing                                 | 12 (4.7) | 10 (5.1)                    | 2 (3.5)                  |         |
| Ever used family planning? n (%)        |           |                             |                          | 0.33    |
| Yes                                     | 151 (59.7)| 121 (62.0)                  | 30 (51.6)                |         |
| No                                      | 94 (37.1)| 68 (34.9)                   | 28 (44.8)                |         |
| Missing                                 | 8 (3.2)   | 6 (3.1)                     | 2 (3.5)                  |         |
| **Medical and lifestyle**               |           |                             |                          |         |
| History of diabetes mellitus, n (%)     |           |                             |                          | 0.18    |
| Yes                                     | 7 (2.8)   | 7 (3.6)                     | 0 (0.0)                  |         |
| No                                      | 114 (45.1)| 91 (46.7)                   | 23 (39.7)                |         |
| Missing                                 | 132 (51.1)| 97 (49.7)                   | 35 (60.3)                |         |
| History of hypertension, n (%)          |           |                             |                          | 0.32    |
| Yes                                     | 55 (21.7)| 46 (23.6)                   | 9 (15.5)                 |         |
| No                                      | 69 (27.3)| 54 (27.7)                   | 15 (25.9)                |         |
| Missing                                 | 129 (51.0)| 95 (48.7)                   | 34 (58.6)                |         |
Table 1. Continued

| Characteristic                              | Total=253 | Regular menopause Total=195 | Early menopause Total=58 | P-value |
|---------------------------------------------|-----------|----------------------------|--------------------------|---------|
| **Ever smoked cigarettes, n (%)**          |           |                            |                          | 0.58    |
| Yes                                         | 8 (3.2)   | 7 (3.6)                    | 1 (1.7)                  |         |
| No                                          | 236 (93.3)| 182 (93.3)                 | 54 (93.1)                |         |
| Missing                                     | 9 (3.5)   | 6 (3.1)                    | 3 (5.2)                  |         |
| **Ever drank alcohol, n (%)**               |           |                            |                          | 0.07    |
| Yes                                         | 86 (34.0) | 71 (36.4)                  | 15 (25.9)                |         |
| No                                          | 164 (64.8)| 123 (63.1)                 | 41 (70.7)                |         |
| Missing                                     | 3 (1.2)   | 1 (0.5)                    | 2 (3.4)                  |         |
| **Body mass index (kg/m²), median (IQR)**   |           |                            |                          | 0.55    |
| Regular menopause                           | 26.5 (23.1–32.4) | 28.0 (23.0–32.8) | 26.1 (24.3–29.0) |         |
| Early menopause                             |           |                            |                          |         |
| **HIV and co-morbidities**                  |           |                            |                          |         |
| HIV status, n (%)                           |           |                            |                          | 0.001   |
| Negative                                    | 34 (13.4) | 33 (16.9)                  | 1 (1.7)                  |         |
| Positive                                    | 219 (86.6)| 162 (83.1)                 | 57 (98.3)                |         |
| **Median duration of HIV diagnosis, years (IQR)** | 5 (4–7) | 5 (4–7)                    | 5 (3–6)                  | 0.01    |
| **Median baseline CD4 cell count, cells/mm³ (IQR)** | 216 (138–291) | 207 (136–294) | 223 (157–287) | 0.84    |
| **CD4 cell category at baseline, cells/mm³** |           |                            |                          | 0.85    |
| ≥350                                        | 24 (11.0) | 18 (11.1)                  | 6 (10.5)                 |         |
| 200–349                                      | 89 (40.6) | 62 (38.3)                  | 27 (47.4)                |         |
| 100–199                                      | 59 (26.9) | 47 (29.0)                  | 12 (20.1)                |         |
| 50–99                                        | 24 (11.0) | 18 (11.1)                  | 6 (10.5)                 |         |
| ≤49                                         | 14 (6.4)  | 10 (6.2)                   | 4 (7.0)                  |         |
| **Baseline HIV RNA, copies/mL (IQR)**       | 64,094 (13,358–196,125) | 52,984 (11,142–188,044) | 103,914 (20,695–440,770) | 0.08    |
| HIV RNA >100,000 copies/mL                  | 73 (33.3) | 47 (29.0)                  | 26 (45.6)                | 0.008   |
| **WHO stage**                               |           |                            |                          | 0.85    |
| I                                           | 74 (33.8) | 54 (33.3)                  | 20 (35.1)                |         |
| II                                          | 53 (24.2) | 38 (23.5)                  | 15 (26.3)                |         |
| III                                         | 54 (24.7) | 39 (24.1)                  | 15 (26.3)                |         |
| IV                                          | 9 (4.1)   | 8 (4.9)                    | 1 (1.8)                  |         |
| Missing                                     | 29 (13.2) | 23 (14.2)                  | 6 (10.5)                 |         |
| **Anti-HCV Ab positive, n (%)**              |           |                            |                          | 0.42    |
| Positive                                    | 41 (18.7) | 27 (16.7)                  | 14 (24.6)                |         |
| Negative                                    | 158 (72.2)| 120 (74.1)                 | 38 (66.7)                |         |
| Missing                                     | 20 (9.1)  | 15 (9.3)                   | 5 (8.7)                  |         |
| **HBsAg positive, n (%)**                   |           |                            |                          | 0.37    |
| Positive                                    | 29 (13.2) | 22 (13.6)                  | 7 (12.3)                 |         |
| Negative                                    | 163 (74.4)| 123 (75.9)                 | 40 (70.2)                |         |
| Missing                                     | 27 (12.3) | 17 (10.5)                  | 10 (17.5)                |         |
| **Prior ART experience, n (%)**             |           |                            |                          | 0.27    |
| Yes                                         | 31 (14.2) | 26 (16.1)                  | 5 (8.8)                  |         |
| No                                          | 175 (79.9)| 125 (77.2)                 | 50 (87.7)                |         |
| Missing                                     | 13 (5.9)  | 11 (6.8)                   | 2 (3.5)                  |         |
| **Follow-up data**                          |           |                            |                          |         |
| Use of HAART, n (%)                         |           |                            |                          | 0.77    |
| Yes                                         | 205 (93.6)| 150 (92.6)                 | 55 (96.5)                |         |
| No                                          | 10 (4.6)  | 8 (4.9)                    | 2 (3.5)                  |         |
| Missing                                     | 4 (1.8)   | 4 (2.5)                    | 0 (0.0)                  |         |
| **Median duration of HAART use, years (IQR)** | 5 (3–6) | 5 (4–6)                    | 4 (3–6)                  | 0.003   |
| **Current median CD4, cells/mm³ (IQR)**     | 469 (312–663) | 468 (317–663) | 481 (312–661) | 0.97    |
| **Current HIV RNA*, n (%)**                 |           |                            |                          | 0.48    |
| Undetectable                                | 128 (75.3)| 97 (74.1)                  | 31 (79.5)                |         |
| Detectable                                  | 42 (24.7) | 34 (25.9)                  | 8 (20.5)                 |         |

* Limit of detection <400 copies/mL. Available for 170 HIV-positive subjects
to subjects with regular natural menopause, those with early menopause were younger \((P<0.001)\), more likely to be unemployed \((P<0.001)\), attained menarche earlier \((P=0.03)\) and were more likely to be HIV positive \((P=0.001)\). Among subjects infected with HIV, women with EM had shorter duration of HIV diagnosis \((P=0.01)\), higher rates of hepatitis C virus co-infection \((P=0.009)\), and shorter duration of HAART use \((P=0.003)\).

The results of bivariate and multivariate analyses for factors associated with EM are shown in Table 2. Following adjustment for confounders, the odds of experiencing early menopause were 2.37 (95% CI 1.24–4.52) for sexually active subjects and 10.95 (95% CI 1.39–86.33) for HIV-positive subjects in the combined cohort. Among HIV-positive subjects, early menarche (AOR=14.88, 95% CI 1.37–161.10) and sexual activity (AOR=2.02, 95% CI

| Table 2. Unadjusted and adjusted odds ratios (OR) for early menopause (age ≤45 years) among women in Jos, Nigeria \((n=253)\) |
| --- |
| Characteristic | All subjects \((n=253)\) | HIV-infected subjects \((n=219)\) |
| | Crude OR | Adjusted OR | Crude OR | Adjusted OR |
| | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Employment status | | | | |
| Unemployed | Ref | Ref | Ref | Ref |
| Employed | 0.40 (0.20–0.78) | 0.002 | 0.60 (0.30–1.23) | 0.16 |
| Alcohol use | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 0.60 (0.31–1.17) | 0.06 | 0.54 (0.27–1.09) | 0.08 |
| Early menarche | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 10.58 (1.07–103.75) | 0.001 | 10.20 (0.99–104.21) | 0.05 |
| Sexual activity | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 1.74 (0.95–3.19) | 0.03 | 2.37 (1.24–4.52) | 0.008 |
| HIV status | | | | |
| Negative | Ref | Ref | Ref | Ref |
| Positive | 11.61 (1.55–86.85) | 0.001 | 10.95 (1.39–86.33) | 0.02 |
| HCV co-infection | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 1.62 (0.78–3.38) | 0.10 | 1.89 (0.88–4.08) | 0.10 |
| Prior HAART use | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 0.50 (0.18–1.37) | 0.08 | 1.46 (0.49–4.28) | 0.48 |
| HAART use <5 years | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 1.83 (1.00–3.38) | 0.02 | 1.29 (0.43–3.86) | 0.63 |
| HIV diagnosis <5 years | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 1.74 (0.95–3.08) | 0.03 | 1.43 (0.47–4.33) | 0.91 |
| HIV RNA >100,000 copies/mL | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 0.59 (0.31–1.60) | 0.04 | 1.84 (0.9–3.71) | 0.91 |
| AIDS at enrolment* | | | | |
| No | Ref | Ref | Ref | Ref |
| Yes | 1.78 (0.35–8.51) | 0.36 | 0.91 (0.17–4.89) | 0.08 |
| CD4 category (cells/mm³) | | | | |
| ≥350 | Ref | Ref | Ref | Ref |
| 200–349 | 1.30 (0.46–3.65) | 0.64 | 1.30 (0.43–3.96) | 0.51 |
| 100–199 | 0.76 (0.24–2.34) | 0.67 | 0.67 (0.20–2.22) | 0.51 |
| 50–99 | 1.00 (0.27–3.69) | 1.00 | 0.80 (0.19–3.32) | 0.76 |
| ≤49 | 1.20 (0.27–5.28) | 0.80 | 1.23 (0.24–6.19) | 0.79 |

* WHO stage IV disease
One limitation of this study was its cross-sectional nature and our understanding of the factors that put women at increased risk. In a study comparing HIV-positive and negative women, HIV infection was reported to be a risk factor for age at menarche, pregnancy, and EM in this study, HIV-seropositive women are exposed to multiple stressors, a phenomenon known to cause amenorrhoea and EM. In conclusion, EM was common in our cohort and was associated with HIV infection, early menarche and sexual activity. As the population of HIV-infected women experiencing menopause grows, guidelines for the management of this important aspect of ageing should be incorporated into routine HIV care.

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Discussion

Early menopause is the first step in a chain of causality leading to tissue or organ dysfunctions and lesions via hormonal mechanisms [29]. Early menopause is harmful to the overall health of women and has been associated with alterations in mood and sexual function, declines in quality of life, development of comorbidities such as cardiovascular disease, osteoporosis and fragility fractures, and increased risk for all-cause mortality [23,30,31].

In this study, we found HIV infection, early menarche and sexual activity to be independently associated with EM, with HIV-infected women having significantly higher rates of EM. The high rates of EM obtained in this study have been similarly reported in previous studies, which focused on HIV-positive women [20,21,32]. However, lower prevalences have also been reported by an Italian study among HIV-infected women [33] as well as a large study conducted in the United Kingdom among women in the general population [34]. The association between HIV infection and EM is likely multifactorial and subject to confounding by other factors. Studies have shown that many of the factors associated with EM are more prevalent in HIV-positive patients and can affect the onset of early natural menopause. A study that examined the occurrence of prolonged amenorrhoea and ovarian failure found HIV infection to be associated with a three-fold increased risk of prolonged amenorrhoea without ovarian failure [35]. HIV-infected women have also been reported to have a higher risk of menstrual irregularities, anovulation and amenorrhoea [36,37] and these factors impact on the ability of healthcare providers to accurately assess the onset/occurrence of early menopause in the absence of biochemical parameters.

Given the negative impact that EM has on women’s health, an understanding of the factors that put women at increased risk for EM is important for enhanced counselling and optimisation of their health. In a study comparing HIV-positive and negative women, HIV infection was reported to be a risk factor for age at natural menopause [19], with HIV-infected women being significantly younger than their negative counterparts. Other factors that have been documented as risk factors for EM include but are not limited to ethnicity/race [31], lifestyle variables [38], reproductive and early-life events [21,31,33,39]. Among HIV-infected women, additional risk factors for EM include immunologic status, history of AIDS-defining illness, and other HIV-associated comorbidities [19,21,32]. Even though we did not document any significant association between HIV-related factors and EM in this study, HIV-seropositive women are exposed to multiple stressors, a phenomenon known to cause amenorrhoea by increasing levels of corticotropin-releasing factor, which subsequently reduces gonadotropin-releasing hormone [37]. It is also possible that with effective immune reconstitution and optimal suppression of viral replication following combination antiretroviral therapy, the magnitude of effect of HIV-related factors on our defined outcome may be diminished. There is literature to support HIV infection as a cause of premature ovarian failure and early menopause. One study suggests an increase in serum FSH levels in sero-positive women when compared to controls, and a study of 24 HIV-positive women aged 20–42 years reported a serum FSH level consistent with menopause in 8% [35].

One limitation of this study was its cross-sectional nature and our reliance on self-report of menopause, which is subject to recall bias. Although previous studies have indicated that menopause is reasonably well recalled, the tendency for recall error increases with time elapsed after the final menstrual period [40]. A second limitation of this study was that no hormonal tests were conducted to confirm menopausal status. Even though the World Health Organization defines menopause based on self-report of cessation of menstruation, this may be insufficient for women living with HIV given the high rates of menstrual irregularities and anovulation experienced by this group of women.

Our study assessed EM among an indigenous African population of HIV-infected women. Given the scarcity of data on HIV and menopause in sub-Saharan Africa, where the majority of the world’s population of HIV-infected women reside, this study provides important data that will guide future research on the menopause transition in our region. We were able to match our HIV-infected population with HIV-negative controls, thus providing more balanced results.

In conclusion, EM was common in our cohort and was associated with HIV infection, early menarche and sexual activity. As the population of HIV-infected women experiencing menopause grows, guidelines for the management of this important aspect of ageing should be incorporated into routine HIV care.
Early menopause in Nigerian women