Maturitas 187 (2024) 108069

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

The association of menopause with cardiometabolic disease risk factors in women living with and without HIV in sub-Saharan Africa: Results from the AWI-Gen 1 study

Raylton P. Chikwati [a,b,*], Nicole G. Jaff [a], Nasrin Goolam Mahyoodeen [c], Lisa K. Micklesfield [d], Michéle Ramsay [b], F. Xavier Gómez-Olivé [e], Shukri F. Mohamed [f], Solomon S.R. Choma [g], Jaya A. George [a,h,i], Nigel J. Crowther [a,i]

[a] *Department of Chemical Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[b] *Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[c] *Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[d] *SAMRC/Wits Developmental Pathways for Health Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[e] *Medical Research Council/Wits University Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
[f] *Chronic Disease Management Unit, African Population and Health Research Center, Nairobi, Kenya*
[g] *Department of Pathology, DIMAMO Population Health Research Centre, University of Limpopo, Polokwane, South Africa*
[h] *The Diagnostic Innovation Hub (DIH), University of the Witwatersrand, Johannesburg, South Africa*
[i] *Department of Chemical Pathology, National Health Laboratory Service, Johannesburg, South Africa*

ARTICLE INFO

Keywords:
Midlife women
Cardiometabolic disease risk factors
HIV
Postmenopause
Premenopause
AWI-Gen

ABSTRACT

Background: Menopause and HIV are associated with cardiometabolic disease. In sub-Saharan Africa there is a growing population of midlife women living with HIV and a high prevalence of cardiometabolic disease.
Objectives: The aim of this study was to determine whether menopause and HIV were associated with cardiometabolic disease risk factors in a population of midlife sub-Saharan African women.
Study design: This was a cross-sectional comparison of cardiometabolic disease risk factors between 944 premenopausal women (733 living without HIV and 211 living with HIV) and 1135 postmenopausal women (932 living without HIV and 203 living with HIV) in sub-Saharan Africa.
Main outcome measures: Anthropometric and cardiometabolic variables were compared between pre- and postmenopausal women living without HIV and between pre- and postmenopausal women living with HIV and between women living without HIV and women living with HIV.
Results: The prevalence of HIV was 19.9 %. Age at menopause was lower in women living with HIV than in women living without HIV (48.1 ± 5.1 vs 50.9 ± 4.7 years, $p < 0.001$).
Women living with HIV and receiving efavirenz-based antiretroviral therapy had a lower body mass index (BMI), hip circumference, blood pressure and carotid intima media thickness but higher triglyceride levels and insulin resistance than women living without HIV. Antiretroviral therapy-naïve women living with HIV had lower HDL-cholesterol than women living without HIV.
In this study, menopause was associated with higher LDL-C levels, regardless of HIV status.
Conclusion: The high prevalence of obesity and related cardiometabolic disease risk factors in these midlife sub-Saharan African women is not related to the menopausal transition. The association of cardiometabolic disease risk factors with HIV and antiretroviral therapy is complex and requires further investigation in longitudinal studies, as does the negative association of age at final menstrual period with HIV.

* Corresponding author at: Department of Chemical Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.
E-mail addresses: raylton.chikwati@wits.ac.za (R.P. Chikwati), nrj1@mweb.co.za (N.G. Jaff), mahyoodeen@yahoo.com (N.G. Mahyoodeen), Lisa.Micklesfield@wits.ac.za (L.K. Micklesfield), Michele.Ramsay@wits.ac.za (M. Ramsay), F.Gomez-OliveCasas@wits.ac.za (F.X. Gómez-Olivé), smohamed@aphrc.org (S.F. Mohamed), solomon.choma@ul.ac.za (S.S.R. Choma), Jaya.george@wits.ac.za (J.A. George), nigel.crowther@nhls.ac.za (N.J. Crowther).

https://doi.org/10.1016/j.maturitas.2024.108069
Received 20 February 2024; Received in revised form 1 July 2024; Accepted 16 July 2024
Available online 17 July 2024
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1. Introduction

The eastern and southern regions of sub-Saharan Africa (SSA) remain disproportionately affected by the human immunodeficiency virus (HIV), accounting for approximately 55 % of the cases globally [1]. Furthermore, the association between HIV and increased risk of comorbidities including cardiometabolic disease (CMD) has been gaining global attention [2,3]. It has been reported that individuals living with HIV have nearly double the risk for CMD than those without HIV [4] and that women living with HIV experience higher CMD risk than men living with HIV [2,3,5].

The prevalence of HIV in midlife SSA women has been reported to be high, above 20 % in one South African study [6]. Moreover, there is a high prevalence of obesity in midlife SSA women, which has been associated with metabolic disorders such as diabetes mellitus, hypertension, and the metabolic syndrome [7]. Menopause has also been associated with increased CMD risk through changes in sex hormones, and lifestyle factors [8]. Combined with a growing population of menopausal women within SSA, it is apparent that the aetiology of cardiometabolic disease (CMD) in the region is complex given that HIV and its therapy have also been shown to be associated with higher risk for both cardiovascular and cardiometabolic diseases [9]. However, the combined effect of HIV, menopause and obesity has not been studied among midlife SSA women.

A meta-analysis on the few SSA studies focusing on the effects of HIV with or without antiretroviral therapy (ART) reported an increased risk for CMD [10]. In addition, HIV has been associated with earlier age at menopause in non-SSA studies which is linked to higher CMD risk [11]. Thus, the interaction between HIV and menopause and its effect on CMD risk is complex but is a neglected area of research within SSA. An understanding of this interaction is vital as it will provide information on the contribution of HIV and menopause to the high prevalence of obesity and associated CMDs observed in midlife SSA women. This study therefore aimed to investigate the differences in CMD risk factors between pre- and postmenopausal women living with HIV (WLWH) and between pre- and postmenopausal women living without HIV (WLWOH) in SSA. We also investigated the interaction between HIV and menopausal status on the levels of CMD risk factors and compared age at menopause between midlife WLWH and WLWOH.

2. Methods

2.1. Study population

This population based cross-sectional study is part of the first phase of the Africa-Wits International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) Partnership for Genomic studies (AWI-Gen 1 study) [12]. We selected 2079 women from three of the six AWI-Gen study sites based on their high prevalence of HIV and availability of menopausal staging data: Nairobi in Kenya and DIMAMO (formerly Dikgale) and Soweto in South Africa.

The recruitment of AWI-Gen study participants has been previously detailed [12]. In summary, a genetically diverse population of approximately 12,000 participants aged 40–60 years including both men and women were randomly selected from the general population from six study sites based in the four countries of Kenya, South Africa (3 sites), Ghana, and Burkina Faso. For the present study, we excluded all men (n = 5405) and all women from Ghana (n = 1091) and Burkina Faso (n = 1039), where HIV was nearly completely absent, perimenopausal women (n = 421), women who refused an HIV test (n = 232), and women with missing menopausal staging data (n = 1170). As a result, 2079 women were recruited for the current study.

2.2. Study variables

Questionnaires were used to gather information on menopause stage, demographics (socioeconomic status and level of education) and behaviour (dietary intake, alcohol consumption, and smoking). Data on dietary intake and alcohol consumption were not collected in Soweto.

A voluntary HIV rapid antibody test (Alere Determine HIV-1/2; Alere San Diego Inc., San Diego, CA) was offered to all study participants. WLWH were asked if they were receiving ART or not. Data on the treatment of hypertension and diabetes mellitus were also collected.

Menopausal stage was defined by asking each woman about her menstrual bleeding patterns. Premenopausal women were defined as having regular menstrual cycles, while perimenopausal women were defined as having irregular menses within the past 12 months and postmenopausal women had experienced amenorrhea for at least twelve consecutive months, or more [13]. Perimenopausal women were excluded to effectively separate individuals who had experienced the menopause transition and those that had not. Age at final menstrual period (FMP) was calculated as the difference between age at recruitment and self-reported years since last menses.

The methodologies on the collection of anthropometric and CMD risk factor measurements by trained staff have been previously described [12]. The study variables collected included height, weight, waist and hip circumference, ultrasound-derived abdominal subcutaneous (SAT), visceral fat (VAT) and carotid intima media thickness (cIMT), systolic and diastolic blood pressure (SBP and DBP), and total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, glucose, and insulin levels. cIMT measurements were not collected in Soweto. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation [14]. Insulin resistance was estimated using the HOMA methodology [15]. All laboratory tests were performed in the same laboratory at the Developmental Pathways for Health Research Unit at the Chris Hani Baragwanath Academic Hospital in Soweto, South Africa.

2.3. Statistical analyses

Parametric continuous data were presented as means ± standard deviations (SD) and non-parametric data as medians and interquartile ranges (IQR). Continuous data were compared between groups using the appropriate parametric (Student's unpaired *t*-test or one-way ANOVA) or non-parametric (Mann–Whitney *U* test or Kruskal–Wallis ANOVA) statistical tests. Categorical data were presented as numbers with percentages. Comparisons of categorical data between groups were performed using either the Chi-squared or Fisher exact test, as appropriate. Non-parametric continuous dependent variables were log transformed to normality before being analysed using multivariable linear regression analyses.

The study population was divided into WLWOH and WLWH and within each of those groups multivariable linear regression was used to determine the association between CMD risk factors, namely SBP, DBP, BMI, waist and hip circumference, VAT and SAT, triglycerides, LDL-C, HDL-C, glucose, insulin resistance (HOMA-IR) and cIMT (dependent variables) between pre- and postmenopausal women (independent variable). A similar approach was repeated to determine the association between the same dependent variables listed above between three groups i.e. WLWOH, WLWH-ART naive, and WLWH receiving ART (WLWH ART+). All these models were adjusted for age and other possible confounding variables which were chosen based on biological plausibility (see Supplemental Table 1). Due to the missing data on dietary intake and alcohol consumption for Soweto two separate regression models were performed for each CMD risk factor with and without Soweto.

Multivariable linear regression models were also used to determine if there was any interaction between HIV status (positive or negative) and menopausal stage. A regression model was set up for each dependent variable (see above) and included HIV status, menopausal stage and an HIV*menopause interaction term as independent variables and with adjustment for possible confounders (Supplemental Table 1). In addition, participants who reported the use of therapies for the treatment of diabetes mellitus or hypertension were excluded from these analyses to minimise the input of drug effects into the regression models. For all regression models, collinearity of variables was assessed using the variance inflation factor (VIF) and in all models the VIFs were found to be <3.

Pearson univariate correlation analysis was used to determine the relationship between the calculated age at FMP and the self-reported years since FMP. Postmenopausal participants were divided into four groups based on years since calculated FMP i.e., ≤3 years, >3 to ≤6 years, >6 to ≤9 years and >9 years, and an ANOVA was used to compared age at FMP between WLWH and WLWOH in each of those four groups. Multivariable linear regression with age at FMP as the dependent variable was performed to investigate if differences in the age at FMP between WLWH and WLWOH were maintained after adjusting for possible confounders i.e., BMI, physical activity, socioeconomic status, level of education, smoking status, and ART status. All analyses were performed using Stata 18 (StataCorp LP, College Station, TX, USA) and the level of statistical significance was set at a two-tailed $p < 0.05$.

3. Results

3.1. Participant characteristics

A total of 2079 women were recruited, with 1665 WLWOH (733 pre- and 932 postmenopausal) and 414 WLWH (211 pre- and 203 postmenopausal) from two study sites in South Africa (DIMAMO and Soweto) and one in Kenya (Nairobi). The HIV prevalence at these sites was 22.2 %, 20.6 % and 17.5 %, respectively. In total, 79 % of the WLWH were receiving ART. At the time of recruitment (2011–2014), participants were receiving the efavirenz-tenofovir-lamivudine combination therapy as per the national guidelines for first-line ART in South Africa and Kenya [16,17]. Supplemental Table 1 shows that WLWH were younger, consumed more alcohol, and were at a lower socioeconomic status than WLWOH. No differences were observed on smoking status, physical activity and the level of education.

3.2. HIV, menopause and CMD risk

When CMD risk factors were compared between pre- and postmenopausal WLWOH, the adjusted analyses showed that the postmenopausal stage was only associated with higher levels of total cholesterol and LDL-C (Table 1). When additional confounders; dietary intake and alcohol consumption which were unavailable for Soweto were added, these differences were no longer statistically significant (data not shown). When these analyses were repeated in WLWH, there were no differences in the levels of CMD risk factors between pre- and postmenopausal women (Table 1).

CMD risk factors were also compared between the three HIV groups i.e. 1665 WLWOH, 240 WLWH ART+ and 61 ART naïve WLWH (excluding 113 WLWH whose ART status was unknown). The results showed that WLWH ART+ had lower BMI, hip circumference, blood pressure, cIMT, but elevated triglycerides and greater insulin resistance than WLWOH, after adjusting for confounding variables (Table 2). These associations were maintained even after adjusting for dietary intake and alcohol consumption (data not shown), except for hip circumference which was no longer significant in these analyses. ART naïve WLWH had lower HDL-C than WLWOH (Table 2). When further adjustments were made for dietary intake and alcohol consumption, ART naïve WLWH had lower BMI (27.6 ± 7.7 vs. 29.6 ± 7.3 kg/m^2, $p = 0.006$), and SAT (1.82 ± 0.99 vs. 2.14 ± 0.88 cm, $p = 0.02$) than WLWOH.

Table 3 shows the adjusted relationship between CMD risk factors and menopause (post- vs premenopause), HIV status (positive vs negative) and the HIV*menopause interactions. Menopause was only associated with slightly higher LDL-C levels (Table 3). When dietary intake and alcohol consumption were adjusted, the association between menopause and LDL-C remained statistically significant (Supplemental Table 2). None of the other CMD risk factors differed between the menopausal groups after adjusting for multiple confounders including HIV status and menopause*HIV interactions (Table 3). HIV was

Table 1
Comparison of CMD risk factors between pre- and postmenopausal women living without and women living with HIV after adjustment for possible confounding variables.

Variables	WLWOH (n = 1665)		WLWH (n = 414)	
	Premenopausal (n = 733)	Postmenopausal (n = 932)	Premenopausal (n = 211)	Postmenopausal (n = 203)
Anthropometry				
BMI (kg/m^2)	30.8 ± 7.3	31.2 ± 7.4	28.0 ± 7.0	27.4 ± 7.1
Hip circumference (cm)	110.6 ± 15.2	111.2 ± 15.6	104.4 ± 14.7	103.5 ± 15.5
Waist circumference (cm)	94.1 ± 15.4	96.7 ± 14.9	88.8 ± 14.3	89.3 ± 14.8
SAT (cm)	2.46 ± 1.07	2.51 ± 1.06	2.18 ± 1.10	2.18 ± 1.07
VAT (cm)	5.34 ± 2.07	5.57 ± 2.15	5.11 ± 2.03	4.93 ± 2.07
Blood pressure				
Systolic (mm Hg)	118.5 (107.0–131.0)	126.5 (113.0–143.0)	117.0 (104.0–128.5)	120.0 (107.0–136.5)
Diastolic (mm Hg)	81.0 ± 13.3	85.2 ± 13.5	78.7 ± 13.4	81.3 ± 13.5
Metabolic				
Total cholesterol (mmol/L)	4.18 ± 0.99	4.56 ± 1.16*	4.02 ± 1.11	4.46 ± 1.22
LDL-C (mmol/L)	2.55 ± 0.81	2.81 ± 0.92*	2.37 ± 0.83	2.65 ± 0.93
HDL-C (mmol/L)	1.16 (0.97–1.40)	1.19 (1.00–1.40)	1.13 (0.91–1.40)	1.16 (1.00–1.45)
Triglycerides (mmol/L)	0.90 (0.64–1.20)	1.03 (0.78–1.41)	0.90 (0.64–1.12)	1.05 (0.78–1.37)
Glucose (mmol/L)	4.81 (4.47–5.33)	4.99 (4.53–5.54)	4.80 (4.45–5.13)	4.80 (4.50–5.42)
HOMA-IR	1.26 (0.62–2.39)	1.48 (0.68–2.79)	1.28 (0.73–2.28)	1.57 (0.66–2.74)
Cardiovascular risk				
cIMT (mm)	0.58 (0.52–0.64)	0.63 (0.56–0.70)	0.55 (0.50–0.61)	0.60 (0.54–0.68)

Data expressed as mean ± SD or median interquartile range (IQR); WLWOH, women living without HIV; WHLH, women living with HIV; BMI, body mass index; SAT, abdominal subcutaneous fat; VAT, abdominal visceral fat; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; cIMT average carotid intima-media thickness; all comparisons were adjusted for age, physical activity, socioeconomic status, level of education; study site, additional adjustments were made for specific variables as shown in Supplemental Table 2.

* $p < 0.05$, post- vs premenopause.

Table 2
Comparison of CMD risk factors between women living without HIV, women living with HIV and receiving ART and women living with HIV but ART naive.

Variables	WLWOH (n = 1665)	WLWH receiving ART (n = 240)	WLWH ART naive (n = 61)
Age (years)	49.6 ± 5.8	47.6 ± 5.5***	47.5 ± 6.0***
Anthropometry			
BMI (kg/m^2)	31.0 ± 7.4	26.1 ± 6.3***	30.8 ± 8.3
Hip circumference (cm)	110.9 ± 15.4	100.4 ± 13.3*	111.9 ± 18.3
Waist circumference (cm)	95.6 ± 15.2	86.9 ± 13.5	92.3 ± 15.4
SAT (cm)	2.49 ± 1.07	2.02 ± 0.99	2.62 ± 1.21
VAT (cm)	5.47 ± 2.11	4.90 ± 2.01	4.98 ± 2.25
Blood pressure			
Systolic (mm Hg)	122.5 (110.0–138.0)	114.5 (102.0–126.3)***	130.0 (114.5–141.0)
Diastolic (mm Hg)	83.4 ± 13.6	76.4 ± 12.6***	86.2 ± 13.3
Metabolic			
Total cholesterol (mmol/L)	4.40 ± 1.11	4.24 ± 1.21	4.08 ± 1.03
LDL-C (mmol/L)	2.69 ± 0.87	2.47 ± 0.90	2.47 ± 0.85
Triglycerides (mmol/L)	1.08 ± 0.54	1.10 ± 0.61*	1.07 ± 0.38
HDL-C (mmol/L)	1.17 (0.99–1.40)	1.16 (0.96–1.48)	1.10 (0.90–1.30)*
Glucose (mmol/L)	4.90 (4.50–5.48)	4.87 (4.50–5.38)	4.80 (4.50–5.10)
HOMA-IR	1.36 (0.65–2.56)	1.41 (0.73–2.52)**	1.21 (0.61–2.33)
Cardiovascular risk			
cIMT (mm)	0.60 (0.54–0.68)	0.56 (0.51–0.63)**	0.58 (0.55–0.68)

Data expressed as mean ± SD or median interquartile range (IQR); WLWOH, women living without HIV; WHLH, women living with HIV; BMI, body mass index; SAT, abdominal subcutaneous fat; VAT, abdominal visceral fat; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; cIMT average carotid intima-media thickness; all comparisons were adjusted for age, physical activity, socioeconomic status, level of education, smoking status, alcohol consumption, vegetable, fruit, soft drink, fruit juice, and bread intake; study site; additional adjustments were made for specific variables as shown in Supplemental Table 2.

* $p < 0.05$ vs WLWOH.

** $p < 0.01$ vs WLWOH.

*** $p < 0.001$ vs WLWOH.

associated with lower hip circumference, BMI, blood pressure and cIMT, but higher triglycerides than in uninfected counterparts. These associations were similar even after adjusting for dietary intake and alcohol consumption, except for insulin resistance which became significantly higher in the WLWH (1.36 (0.64–2.52) vs. 1.25 (0.58–2.37), $p = 0.02$) (Supplemental Table 3). As shown in Table 2, these associations with HIV are largely driven by ART use. Table 3 also shows that there was no evidence of an interaction effect between HIV and menopause status on the CMD risk factors and these observations remained similar after further adjustment for dietary intake and alcohol consumption (Supplemental Table 3).

3.3. Age at FMP and HIV status

When age at FMP was compared between WLWH and WLWOH, it was observed that WLWH reached menopause at an earlier age than their uninfected counterparts (Table 4) (46.8 ± 5.2 vs 48.4 ± 5.6 years, $p < 0.001$). Due to these self-reported low ages for FMP, further analyses were undertaken. Thus, Pearson correlation analysis showed an inverse relationship between age at FMP and the reported years since menopause ($r = -0.59$, $p < 0.001$, $n = 962$), suggestive of an underestimation of age at FMP with increasing years after menopause. This was confirmed when women were divided into four groups based on years since calculated FMP i.e., ≤3 years, >3 to ≤6 years, >6 to ≤9 years and >9 years, and age at FMP was compared between WLWH and WLWOH in each of those 4 groups (Table 4). The age at FMP was always found to be lower in the WLWH group but was only significant in the group within ≤3 years of FMP and in the combined group (Table 4). In addition, the calculated age at FMP fell in both groups the further the women reported that they were from FMP (Table 4). The significant difference in age at FMP between WLWH and WLWOH was maintained for both the combined group and the group who reported that their FMP was within 3 years of their interview in a multivariable linear regression model for FMP which was adjusted for BMI, physical activity, socioeconomic status, education, smoking, and study site (Table 5). Irrespective of HIV status, the regression model also showed differences in the age at FMP across the different sites: Nairobi, 47.2 ± 4.7; DIMAMO 50.1 ± 4.7 and Soweto; 51.6 ± 4.4 years. The differences were significant between Nairobi and DIMAMO ($p < 0.001$) and between Nairobi and Soweto ($p < 0.001$) but not between DIMAMO and Soweto ($p = 0.05$).

4. Discussion

The current study compared CMD risk factors between midlife pre- and postmenopausal WLWH and WLWOH from SSA. The results showed that only LDL-C and total cholesterol levels were higher in post- than premenopausal WLWOH, but no significant associations were observed in WLWH. When investigating the combined effects of menopause, HIV and ART, the relationship between menopause and LDL-C levels remained statistically significant. The presence of HIV was associated with greater triglyceride levels but lower BMI, hip circumference, blood pressure and cIMT. These associations were largely driven by the use of ART. Furthermore, the age at menopause was lower in WLWH than WLWOH.

To our knowledge, this is the first large-scale study to compare CMD risk factors between pre- and postmenopausal women in WLWH and WLWOH. However, there are studies that have focused on WLWH or WLWOH exclusively. Thus, in the REPRIEVE study, with 1449 participants from the US, South Africa, Zimbabwe, Brazil, and Peru, only waist circumference and haemoglobin levels were higher in post- than in premenopausal WLWH [18]. In a Women's Interagency HIV Study (WIHS) sub-analysis, from a US population, blood pressure, BMI, and diabetes were higher in post- than premenopausal women [19] however, age was not adjusted for in this study. Data on CMD risk during the menopause transition in WLWH remain scarce and therefore warrants further investigation. Data on WLWOH, specifically from high-income countries have shown that menopause is associated with increased CMD risk [8]. We also confirmed these associations through a meta-analysis of studies conducted in low- and middle-income countries including a small number from Africa [20]. Furthermore, our previous analyses on the entire AWI-Gen population (n = 3609) showed that menopause-related differences in CMD risk factors were more prominent in West than East and South Africa [21]; the reason for this is not known and requires further investigation. In the present study, only LDL-C was

Table 3
Multivariate linear regression models showing relationship of menopausal stage and HIV status with CMD risk factors for all sites combined.

Dependant variable	Independent variable	Unstandardised β (95 % CI)[*]
Waist circumference (cm)	Menopausal stage[a]	0.71 (−0.30–1.72)
	HIV[b]	0.52 (−0.59–1.64)
	HIV * Menopausal stage	−0.48 (−2.15–1.19)
Hip circumference (cm	Menopausal stage[a]	−0.63 (−1.44–0.18)
	HIV[b]	−1.46 (−2.35 to −0.56)[***]
	HIV * Menopausal stage	0.37 (−0.90–1.64)
BMI (kg/m^2)	Menopausal stage[a]	−0.15 (−1.06–0.77)
	HIV[b]	−3.22 (−4.30 to −2.15)[***]
	HIV * Menopausal stage	−0.17 (−1.74–1.40)
VAT (cm)	Menopausal stage[a]	−0.02 (−0.22–0.18)
	HIV[b]	0.11 (−0.13–0.34)
	HIV * Menopausal stage	−0.10 (−0.44–0.23)
SAT (cm)	Menopausal stage[a]	−0.05 (−0.15–0.06)
	HIV[b]	−0.06 (−0.19–0.06)
	HIV * Menopausal stage	−0.02 (−0.15–0.20)
Diastolic BP (mm Hg)	Menopausal stage[a]	0.14 (−1.72–1.99)
	HIV[b]	−2.30 (−4.23 to −0.38)[*]
	HIV * Menopausal stage	0.58 (−2.19–3.37)
Systolic BP (log; mm Hg)	Menopausal stage[a]	−0.01 (−0.03–0.01)
	HIV[b]	−0.03 (−0.06 to −0.01)[**]
	HIV * Menopausal stage	0.02 (−0.03–0.07)
LDL-C (mmol/L)	Menopausal stage[a]	0.15 (0.04–0.27)[**]
	HIV[b]	−0.05 (−0.20–0.08)
	HIV * Menopausal stage	−0.24 (−0.23 to −0.18)
Triglycerides (log; mmol/L)	Menopausal stage[a]	0.05 (−0.01–0.11)
	HIV[b]	0.10 (0.03–0.18)[**]
	HIV * Menopausal stage	−0.03 (−0.14–0.08)
HDL-C (log; mmol/L)	Menopausal stage[a]	−0.01 (−0.05–0.03)
	HIV[b]	−0.06 (−0.11–0.01)
	HIV * Menopausal stage	0.05 (−0.03–0.13)
Glucose (1/mmol/L)	Menopausal stage[a]	0.005 (−0.0001–0.009)
	HIV[b]	0.003 (−0.002–0.008)
	HIV * Menopausal stage	−0.002 (−0.009–0.05)
HOMA-IR (log)	Menopausal stage[a]	0.02 (−0.13–0.17)
	HIV[b]	0.13 (−0.04–0.29)
	HIV * Menopausal stage	0.06 (−0.18–0.31)
cIMT (log; mm)	Menopausal stage[a]	0.12 (−0.07–0.30)
	HIV[b]	−0.22 (−0.01 to −0.43)[*]
	HIV * Menopausal stage	0.01 (−0.32–0.33)

Data is unstandardised ß co-efficient (95 % confidence intervals); BMI, body mass index; VAT, abdominal visceral fat; SAT, abdominal subcutaneous fat; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; cIMT average carotid intima-media thickness.
[a] Post- vs premenopause.
[b] WLWH vs WLWOH.
[*] $p < 0.05$.
[**] $p < 0.01$.
[***] $p < 0.001$.

significantly different between pre- and postmenopausal groups, but the difference was small (0.15 (0.04–0.27) mmol/L) and possibly of little clinical significance.

In the current study, we have shown that WLWH ART+ had lower BMI than WLWOH as previously shown in a meta-analysis of SSA studies [10]. The association between ART and lower BMI could be attributed to the composition of the ART regimens (efavirenz, tenofovir, and lamivudine) that our study participants were taking. Efavirenz containing regimens have been associated with changes in body fat composition, which include lower trunk, limb and visceral fat [22]. Recent clinical trials conducted in South Africa and Cameroon have also shown that a dolutegravir-based regimen was associated with greater weight gain compared to an efavirenz-based regimen [23,24]. It is suggested that efavirenz-mediated fat loss is due to adipocyte mitochondrial toxicity leading to oxidative stress and subsequent apoptosis [25]. Studies have also highlighted that HIV reduces nutrient absorption and increases protein turnover leading to weight loss [26]. In addition, reduced caloric intake associated with the depression that is sometimes provoked by HIV diagnosis may contribute to weight loss [27].

Table 4
Comparison of calculated age at final menstrual period between women living with and without HIV and stratified by self-reported years since the final menstrual period.

Years since FMP	WLWH		WLWOH		P value
	Age at FMP	n	Age at FMP	n	
≤3 years	48.1 ± 5.1	98	50.9 ± 4.7	428	<0.001
>3 to ≤6 years	47.8 ± 4.7	33	48.5 ± 4.5	137	0.38
>6 to ≤9 years	45.1 ± 4.2	17	45.5 ± 4.8	78	0.71
>9 years	41.4 ± 3.6	24	42.5 ± 4.3	147	0.27
Age groups combined	46.8 ± 5.2	172	48.4 ± 5.6	790	0.001

Data expressed as mean ± SD, and sample size (n); WLWH, women living with HIV; WLWOH, women living without HIV; FMP, final menstrual period.

Table 5
Relationship of HIV status with age at final menstrual period.

Study group	Independent variable	
	HIV status[a] (unadjusted)	HIV status[a] (adjusted)[b]
Postmenopausal women within 3 years of FMP	−2.7 (−3.8 to −1.6)[***]	−2.2 (−3.3 to −1.0)[***]
All postmenopausal women	−1.1 (−2.0 to −0.2)[***]	−1.6 (−2.4 to −0.8)[***]

Data is unstandardised ß (95 % confidence interval) for age at FMP vs HIV status.
[a] HIV status, WLWH vs. WLWOH.
[***] $p < 0.001$.
[b] Adjusted for BMI, physical activity, socioeconomic status, level of education, smoking status, study sites.

The link between ART and insulin resistance has been observed in previous studies [28,29]. The mechanisms behind these associations have been thought to be driven by the effect of ART on insulin signalling or indirectly via lipodystrophy [29,30]. Our findings also show that HIV but not ART was associated with lower HDL-C levels. Other studies have shown similar associations [31,32]. In these studies, HDL-C was directly associated with BMI and CD4+ T-cell counts. Rose et al. further highlighted that reverse cholesterol transport was only impaired among in ART naïve participants [32]. Their findings showed that the activity of cholesteryl ester transfer protein (CETP), which transfers cholesterol esters from HDL-C to LDL-C and VLDL-C while transferring triglycerides to HDL-C was enhanced in the presence of HIV compared to uninfected counterparts. It was therefore proposed that the increase in the rate of transfer of materials between HDL-C and LDL-C and VLDL-C would decrease the formation of nascent HDL-C particles by the liver, and ultimately the subtotal HDL-C concentrations [32].

In the current study, we report lower systolic and diastolic blood pressure in WLWH ART+, but no differences between WLWOH and ART naïve women. Previous investigations on the relationship between blood pressure and ART have been inconclusive, with some reporting positive [33–36], inverse [37,38] or no associations [5,39,40]. These discrepancies may be attributed to the different ART regimens studied. In South Africa for example, Brennan et al. showed that individuals who switched from an efavirenz to a dolutegravir-based ART regimen had higher blood pressure levels than those who never switched [38].

Consistent with our findings, Hanna et al. reported an association between ART and lower cIMT levels but only in the 50–75 age group and not in younger adults (30–49 age group) [41]. Our study also showed that there was no difference in cIMT levels between ART naïve and WLWOH. Other studies from the SSA countries i.e. Uganda [42], Botswana [43] and Ethiopia showed no association between cIMT and ART. Together, there may be several reasons for these inconsistencies. Firstly, most of these studies had relatively smaller sample sizes ranging from 306 to 548 study participants [42–45]. Secondly, the selection of study participants was not uniform; for example in the current study we included both pre- and postmenopausal women, while other studies recruited mostly premenopausal women [42]. In another study, the selection of the WLWOH control group was based on a relatively unhealthy referral group from a hospital clinic [45]. Thirdly, the use of different classes of ART and duration of use could be an additional source of heterogeneity across studies, as some specific ART regimens and their prolonged use have been linked with greater CMD risk than others. Finally, the cross-sectional nature of these studies (including ours) makes it difficult to control for all residual confounding.

In the current study we show that WLWH from South Africa and Kenya experienced menopause earlier (48.1 $\pm$ 5.1 years) than WLWOH (50.9 $\pm$ 4.7 years). Similar findings have been reported in studies outside SSA including Thailand, where WLWH had a mean age at FMP of 47.3 $\pm$ 5.1 years compared to 49.5 $\pm$ 3.6 years for WLWOH [46], and in the United States, where the median age at FMP in WLWH was 46.0 (IQR: 39.0–49.0) years compared to 47.0 (IQR: 44.5–48.0) years in the uninfected group [47]. The reason for a lower age at FMP in WLWH is unclear. However, other studies have reported that severe immunosuppression (CD4+ <200 cells/mm^3), longer duration of HIV infection, and co-infection with hepatitis C may be associated with earlier age at FMP in WLWH [47–49]. Furthermore, one study from Denmark showed that anti-Mullerian hormone (AMH) levels were lower in WLWH than in uninfected premenopausal counterparts [50]. Since AMH is a measure of ovarian reserve, these findings suggest physiological differences that may predispose WLWH to an early age at menopause.

The present study showed that women from Kenya had an earlier age at FMP than both urban and rural women from South Africa. We therefore hypothesise that socio-demographic differences between the South African and Kenyan populations in our study may explain the different age at FMPs observed in these groups. A global meta-analysis showed that higher level of education and occupation were associated with later age at FMP, while smoking was associated with earlier age at FMP [51].

4.1. Strengths and limitations

Study limitations include its cross-sectional format and therefore we could only measure associations but not causality. In addition, we were unable to ascertain whether WLWH were infected before or after their FMP, given the cross-sectional nature of this study. We did not have data on the duration of HIV infection and ART use, and measurements on viral load and CD4 counts. Participants were recruited between 2013 and 2016, a period during which national guidelines recommended an efavirenz-based regimen for people living with HIV. While this regimen is still being prescribed, the updated national guidelines have transitioned toward a dolutegravir-based regimen. Consequently, the scope of our study regarding new ART regimens may be restricted. We did not collect data on menopausal hormone therapy, oral contraception, and the use of hormone intrauterine devices which are associated with amenorrhea. As a result, this may limit the accuracy of the data on FMP. Lastly, we had a small sample size when comparing variables across HIV groups. There is therefore a need to repeat these analyses in a larger study focused entirely on pre- and postmenopausal women with and without HIV. Despite these limitations, our study is currently the largest cross-sectional analysis of HIV, menopause and CMD in SSA. In addition, we measured a large number of study variables, and all biochemical assays were conducted in a single laboratory to ensure standardisation.

4.2. Conclusions

In this specific study population we demonstrated that the postmenopausal stage was not associated with CMD risk factors (except for LDL-cholesterol) regardless of HIV status and these findings suggest that within this cohort of midlife women from SSA, menopause was not a principal driver of obesity and related CMDs. Our findings also demonstrated that WLWH may have an earlier age at FMP than WLWOH and this requires further examination to determine whether this translates into higher CMD risk after the menopause transition. The differential associations of ART use with CMD risk factors observed in this study require further investigation in longitudinal analyses that consider the ART regimens in current use.

Contributors

Raylton P. Chikwati contributed to statistical analyses, drafting, and critical revision of the manuscript.

Nicole G. Jaff contributed to collection and interpretation of data and critical revision of the manuscript.

Nasrin Goolam Mahyoodeen contributed to interpretation and critical revision of the manuscript.

Lisa K. Micklesfield contributed to data collection in Soweto, guidance on statistical analyses, interpretation of data and critical revision of the manuscript.

Michéle Ramsay contributed to the conception and design of the study, interpretation of data and critical revision of the manuscript.

F. Xavier Gómez-Olivé contributed to interpretation of data and critical revision of the manuscript.

Shukri F. Mohamed contributed to data collection in Nairobi and critical revision of the manuscript.

Solomon S.R. Choma contributed to data collection in DIMAMO and critical revision of the manuscript.

Jaya A. George contributed to the interpretation of data and critical revision of the manuscript.

Nigel J. Crowther contributed to the conception and design of the study, guidance on statistical analyses, interpretation of data and critical revision of the manuscript.

All authors approved the final version of the manuscript for submission.

Funding

The data collection was funded by the National Institutes of Health (NIH) under the umbrella of the H3Africa Consortium (NIH U54HG006938 and its supplements), blood marker assays were co-funded by additional funding from the South African Department of Science and Technology (now Department of Science and Innovation) (DST/CON 0056/2014), and RPC received a bursary from Shimadzu South Africa (Pty) Ltd. The views expressed in this paper are those of the authors and do not necessarily reflect the views of the funders. The funders of this study had no role in study design, collection, analysis, management, and interpretation, or in the writing of the manuscript and the decision to submit the manuscript.

Ethical approval

Ethical approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand for the AWI-Gen study (M121029 and M170880) and for the current sub-study (M2010106). In addition, local ethical approval was obtained in the respective AWI-Gen study sites. All study participants provided written informed consent.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.
Data sharing and collaboration

The AWIGen phenotype data have been submitted to the European Genome-Phenome Archive (EGA), accession number EGA00001002482 [52]. The Human Heredity and Health in Africa (H3Africa) Data and Biospecimen Access Committee (DBAC) will review requests for the AWI-Gen phenotype dataset. Related documents including study protocol and statistical analysis plan will be available upon request from the corresponding author.

Declaration of competing interest

The authors declare that they have no competing interest.

Acknowledgements

We would like to acknowledge the AWI-Gen participants, H3Africa Consortium and the study coordinators and field teams at the study sites and the funders of this work (NIH U54HG006938 and its supplements, and DST/CON 0056/2014).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.maturitas.2024.108069.

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