Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Calvet GA. et al. (2015) Predictors of early menopause in HIV-infected women: a prospective cohort study. *Am J Obstet Gynecol*. 212(6):765.e1-765.e13.
Date of Review:	March 9, 2016
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☒ **Social Science** ☐ **Programmatic Review** ☐
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other: HIV, menopause** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population: HIV infected women** **Setting: Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin: Brazil** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Primary research; to determine the age at natural menopause and its predictors in human immunodeficiency virus-infected women in Rio de Janeiro, Brazil.
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Data was not used for decision-making.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☒	☐	☐	Results can be generalized to all HIV infected women.

Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	
The research study/tool/data dictionary is easily accessed/available electronically	☐	☒	☐	Purchase required for 24 hour access at http://www.ajog.org/article/S0002-9378(14)02499-5/abstract
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	Cost effective analysis was not conducted.
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☒	☐	☐	Costs include specimen collection for Pap smears and colposcopy procedure for all women at baseline to evaluate for any abnormal cytology.
How is the research study/tool funded? ***Please got to Comments section***	☐	☐	☐	No funding stated
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- Chronic HCV infection was significantly associated with earlier age at natural menopause.
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☒	☐	☐	Study was conducted within the Instituto de Presquisa Clinca Evandro Chagas HIV/AIDS Women's Cohort that was established in 1996.
Are these data regularly collected at and/or below a national level?	☐	☒	☐	
Are these data collected manually or electronically?	☐	☐	☐	Manually- data was collected using questionnaires and specimens.

RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	American Journal of Obstetrics & Gynecology
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	New data/information

GYNECOLOGY

Predictors of early menopause in HIV-infected women: a prospective cohort study

Guilherme Amaral Calvet, MD, PhD; Beatriz Gilda Jegerhorn Grinsztejn, MD, PhD; Marcel de Souza Borges Quintana, MSc; Monica Derrico, BSc; Emilia Moreira Jalil, MD, PhD; Andrea Cytryn, MD; Angela Cristina Vasconcelos de Andrade, MD, MSc; Ronaldo Ismerio Moreira, MSc; Marcelo Ribeiro Alves, PhD; Valdiléa Gonçalves Veloso dos Santos, MD, PhD; Ruth Khalili Friedman, MD, PhD

OBJECTIVE: This study sought to investigate the age at natural menopause and its predictors in a cohort of human immunodeficiency virus (HIV)-infected women in Rio de Janeiro, Brazil.

STUDY DESIGN: HIV-infected women ≥30 years of age were included. Menopause was defined as having ≥1 year since the last menstrual period. Early age at natural menopause was defined as the onset of menopause at ≤45 years of age. Multivariate Cox proportional hazards analysis was applied.

RESULTS: A total of 667 women were included, and the median age at baseline was 34.9 years (interquartile range, 30.9—40.5 years). In all, 507 (76%) women were premenopausal, and 160 (24%) reached menopause during the observational period; of these, 36 of 160 (27%) had early menopause. The median age at natural menopause was 48 years (interquartile range, 45—50 years). Menarche at <11 years of age (hazard ratio [HR], 2.03; 95% confidence interval [CI], 1.23—3.37), cigarette smoking during the observational period (HR, 1.59; 95% CI, 1.08—2.33), chronic hepatitis C virus (HCV) infection (HR, 2.53; 95% CI, 1.27—5.07), and CD4 count <50 cells/mm^3 (HR, 3.07; 95% CI, 1.07—8.80) were significantly associated with an earlier age at natural menopause. The magnitudes of the effects of menarche at <11 years of age (HR, 2.7; 95% CI, 1.23—5.94), cigarette smoking during the observational period (HR, 3.00; 95% CI, 1.39—6.45), chronic HCV infection (HR, 6.26; 95% CI, 2.12—18.52), and CD4 count <50 cells/mm^3 (HR, 6.64; 95% CI, 1.91—23.20) were much higher and significantly associated with early natural menopause.

CONCLUSION: Early natural menopause was frequent among the HIV-infected women. In addition to menarche and cigarette smoking, which are menopausal factors among women in general, HIV-related immunodeficiency and chronic HCV were additional predictors for an earlier age at natural menopause. Adequate management of HIV in women is critical, as early onset of menopause has been associated with increased morbidity and mortality.

Key words: chronic hepatitis C, cohort studies, early menopause, human immunodeficiency virus, menopause

Cite this article as: Calvet GA, Grinsztejn BGJ, Quintana MSB, et al. Predictors of early menopause in HIV-infected women: a prospective cohort study. Am J Obstet Gynecol 2015;212:765.e1-13.

The worldwide life expectancy has continued to increase in recent decades, even in developing countries, leading to a greater number of individuals aged ≥60 years. The expanded coverage of combination antiretroviral therapy (cART) has led to significant reductions in morbidity and mortality worldwide,[1] as well as in Brazil,[2,3] effectively turning human immunodeficiency virus (HIV) infection into a chronic condition. From 1998 through 2010 in Brazil, an increase in acquired immune deficiency syndrome (AIDS) cases among individuals aged 50-59 years (9.5-16.3/100,000 inhabitants) and >60 years (2.8-5.1/100,000 inhabitants)[4] has led to an increased number of HIV-infected women entering menopause.[5]

Natural menopause is the permanent cessation of menstruation as a consequence of the loss of ovarian follicular activity and is defined as 12 consecutive months without menstrual periods.[6] Early menopause is the permanent cessation of menstruation between 40-45 years of age. This condition affects 5% of women in the general population, whereas premature menopause occurring <40 years of age affects 1% of women.[7]

Age at menopause varies substantially within and across populations,[8] with the mean age at menopause in the developed world[9-11] being typically higher than that observed in the developing world.[12-14] A cross-sectional, population-based study conducted in 1997 through 1998 among 456 Brazilian women between 45-60 years of age selected through area cluster sampling showed a mean age at menopause of 51.2 years,[15] similar to that observed in developed countries.[9-11] Previous studies conducted worldwide, including a cross-sectional study of 96 HIV-infected Brazilian women,[16] have

From Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil.

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Corresponding author: Guilherme Amaral Calvet, MD, PhD. guilherme.calvet@ipec.fiocruz.br

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observed that natural menopause occurs earlier in HIV-infected women, at approximately 46-49 years of age.[16-20]

A number of factors have been proposed as predictors of natural menopause in the general population of women, including genetics, sociodemographics, lifestyle, smoking history, reproductive history, and adult and early childhood health conditions.[9,21-23] However, few studies in the population of HIV-infected women have evaluated factors associated with earlier natural menopause, particularly in low- and middle-income countries.

Earlier menopause has been associated with an increased risk of negative outcomes such as atherosclerosis,[24] cardiovascular disease,[25] stroke,[26] osteoporosis, and fracture[27] in women from the general population. Therefore, identifying the age at menopause and its predictors is critical to the clinical and gynecological management of HIV-infected women, as postmenopausal women living with HIV/AIDS are more vulnerable to comorbidities compared to women in the general population.[28-30]

The purpose of this study was to investigate the age at natural menopause and the potential predictors of menopause in a large, single-center cohort of HIV-infected women in Rio de Janeiro, Brazil.

Materials and Methods

The Instituto de Pesquisa Clínica Evandro Chagas HIV/AIDS Women's Cohort and the study population

This study was conducted within the Instituto de Pesquisa Clínica Evandro Chagas (IPEC) HIV/AIDS Women's Cohort, an open cohort that was established in 1996 at the IPEC, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil. Data from this cohort were published previously.[31-33] Briefly, study visits occurred once per year from 1996 through 2003 and every 6 months thereafter until 2011. Sociodemographic information, lifestyle behavior, reproductive history, gynecologic history, and laboratory data were collected using structured questionnaires, and specimens were obtained for Pap smears and the detection of sexually transmitted diseases. All women were referred for colposcopy during the baseline visit and further evaluation if abnormal cytology was detected. A total of 1002 women with HIV/AIDS were enrolled in the cohort from May 20, 1996, through Dec. 31, 2010.

Women considered at risk for natural menopause were eligible for the study, and the following inclusion criteria were applied: (1) inclusion in the IPEC Women's Cohort from May 20, 1996, through Dec. 31, 2010; (2) premenopausal status; (3) age $\geq$30 years at the time of cohort entry; (4) age $\geq$30 years on Dec. 31, 2010; and (5) history of at least 1 follow-up visit after study entry.

In all, 728 women met the inclusion criteria (time at inclusion [T0]). However, 31 (4.3%) women were lost to follow-up before reaching 30 years of age, and 30 (4.1%) women did not perform a follow-up visit and were excluded from the analysis. As a result, 667 premenopausal women were considered in the analysis of age at natural menopause. Because women >45 years at the time of cohort enrollment (n = 59) were not eligible for the analysis of early age at natural menopause, only 608 of these premenopausal women were included in the analysis of early menopausal age (Figure 1).

Study outcomes and definitions

The study outcomes included age at natural menopause and early age at natural menopause. Menopausal status was determined prospectively during the cohort interviews.

Natural menopause is defined by the World Health Organization (WHO) as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.[6] This condition is clinically recognized after at least 12 months of amenorrhea, at which time the final menstrual period (FMP) is characterized with certainty.[6]

Induced menopause followed by surgical removal of both ovaries (with or without hysterectomy) or iatrogenic ablation of ovarian function (eg, by chemotherapy or radiation) was not considered natural menopause in this study.

Early natural menopause is defined as the natural onset of menopause at an age $\leq$45 years.[34] Premature menopause is defined as menopause occurring age <40 years, according to the WHO definition.[6]

Covariates

Sociodemographic factors

Race/ethnicity, schooling, and monthly family income (in 2011, the Brazilian monthly minimum wage was US$327.92) were self-reported at cohort entry and evaluated as fixed-effect covariates.

Reproductive factors

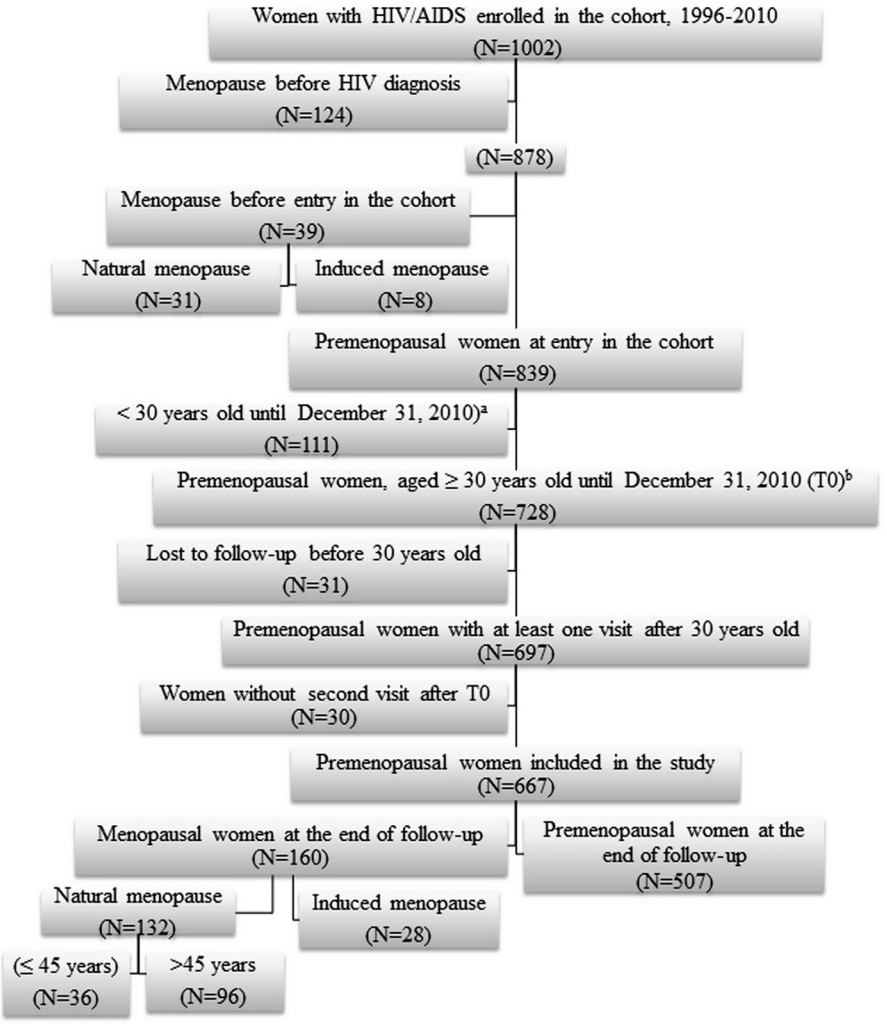
Age at menarche, parity (which was a time-dependent, categorized variable that also took into account the number of children born before study entry), and oral contraceptive or other exogenous hormone exposure (time-dependent variable) were assessed by questionnaire. For oral contraceptive and exogenous hormone exposure, an answer of "yes" corresponded to use at T0 or during the observational period, and an answer of "no" indicated that the women were never exposed.

Lifestyle factors

Alcohol consumption was assessed with the following question at the time of cohort entry: "When you drink, how many distilled or fermented drinks do you ingest?" Frequency of alcohol intake was not evaluated at entry and during the observational period.

Cigarette smoking was assessed through questions about the date of the first and last cigarettes and the number of cigarettes smoked per day. We computed a woman's age at the first and the last cigarette exposure using her birth date. Cigarette smoking was analyzed as 2 time-dependent, categorized covariates, thus allowing a unique point change. The first covariate was cigarette-smoking exposure, which took into account the time of cigarette exposure during the observational period. The second covariate was cigarette exposure in pack-years, which was calculated as the average number of cigarettes smoked per day multiplied by

FIGURE 1
Study profile at Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, 1996 through 2011



[a]Women were included if they were ≥30 years of age at cohort entry or if they turned 30 years of age during follow-up until Dec. 31, 2010; [b]T0 = initial observation period.
AIDS, acquired immune deficiency syndrome; *HIV*, human immunodeficiency virus.
Calvet. Predictors of menopause in HIV-infected women. Am J Obstet Gynecol 2015.

the length of smoking time divided by 20. Time in years from smoking initiation to the outcome or censorship was calculated.

Lifetime illicit drug use was assessed by self-report at cohort entry, with "yes" responses indicating that the women had previously used marijuana, cocaine, crack, glue, or lysergic acid diethylamide (LSD). The use of intravenous and snorted cocaine was evaluated in the statistical inferences.

Health-related factors

Anthropometric data were obtained from the patients' medical charts. The body mass index (BMI) was calculated as the woman's weight (kilogram) divided by the square of her height (meters) and was reported as kg/m^2. BMI was categorized according to WHO standards for adults[35,36] as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), and overweight/obese (≥25.0 kg/m^2). BMI was analyzed as a time-dependent covariate, allowing for multiple changes in value over the study period. BMI at T0 was defined as the value obtained within 6 months of T0.

All other health-related covariates were assessed using the IPEC HIV/AIDS clinical database[37] and were analyzed as time-dependent variables with a unique point change at the date of the diagnosis.

Type 2 diabetes was diagnosed by a fasting plasma glucose ≥126 mg/dL in 2 samples collected on different days or by a 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test.

Chronic hepatitis C virus (HCV) infection was diagnosed following a positive HCV enzyme-linked immunosorbent assay result and confirmed by recombinant immunoblot assay or 2 detectable HCV RNA assays at least 6 months apart.

Hypothyroidism was diagnosed by the presence of at least 1 of the following: goiter, fatigue, cold intolerance, dry skin, constipation, bradycardia, weight gain, changes in menstrual pattern, and decreased levels of thyroxine and triiodothyronine or increased levels of thyroid-stimulating hormone.

HIV/AIDS-related factors

The CD4$^+$ T-cell count was analyzed as a time-dependent and categorized covariate, allowing for multiple point changes over the study period. The CD4$^+$ T-cell count at T0 was described and defined as the value obtained within 6 months of T0. Severe immunodeficiency was defined as a CD4 count <50 cells/mm^3.

The nadir CD4$^+$ T-cell count was determined according to the lowest CD4$^+$ T-cell count available from the time of HIV diagnosis to the end of the observational period.

AIDS-defining illnesses were defined as the presence of any 1993 Centers for Disease Control and Prevention (CDC)-defined AIDS-defining illnesses[38] at any time during the course of HIV infection to the end of the observational period. AIDS-defining illness was assessed as a time-dependent variable.

cART was defined as any lifetime exposure until the end of the observational period to ≥2 nucleoside reverse transcriptase inhibitors and a

nonnucleoside reverse transcriptase inhibitor or at least 1 protease inhibitor.

Statistical analysis

The median (interquartile range [IQR]) and frequency (%) were used to describe the women's characteristics for continuous and categorical data, respectively. Premenopausal women were observed from the time of their cohort entry (for women aged ≥30 years) or from the time they turned 30 years of age (for women aged <30 years at cohort entry) until the end of the observational period (Dec. 31, 2011). This allowed women enrolled in late 2010 to be observed for natural menopause. Women who presented with induced menopause—for example, from hysterectomy, bilateral oophorectomy, chemotherapy, and/or radiotherapy—were censored from the study at the time of menopause, and women who were lost to follow-up before Dec. 31, 2011, were censored from the study at the time of the last gynecological visit. Women were censored from the analysis of early age at natural menopause as they turned 45 years of age, as women of that age are no longer at risk for early menopause.

A Kaplan-Meier model of natural menopause estimated the reverse survival function between natural menopause and age and was defined as the probability of being in natural menopause at the age of 45 and 50 years.

Incidence rates were estimated for both outcomes and reported per 100 person-years. Cox proportional hazards regression analysis using age as a time scale, which adjusts the effects of other covariates by age, which often leads to coefficients with less bias,[39] was used to assess the role of selected covariates on both outcomes. Collinearity between variables was assessed. We fitted the unadjusted models and considered all covariates as statistically significant at the significance level of 20% for age at natural menopause and at 10% for early age at natural menopause as thresholds for the multivariate analysis. A backward elimination method was used, and covariates with the least significant levels were sequentially removed. Covariates statistically significant at 5% ($P < .05$) and those considered as confounders

TABLE 1
Characteristics of 667 participants followed at Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, 1996 through 2011

Characteristic	Total (n = 667)	Natural menopausal women (n = 132)	Early natural menopausal women (n = 36)
Age at baseline, y	34.9 (30.9—40.5)		
Race/ethnicity			
White	264 (39.6)	66 (50.0)	20 (55.6)
Nonwhite	403 (60.4)	66 (50.0)	16 (44.4)
Schooling, y			
>11	72 (10.8)	11 (8.3)	2 (5.6)
>8-11	220 (33.0)	44 (33.3)	13 (36.1)
≤8	375 (56.2)	77 (58.3)	21 (58.3)
Monthly family income[a]	560 (300—1000)		
>5	127 (19.0)	35 (26.5)	9 (25.0)
2-5	215 (32.2)	43 (32.6)	11 (30.6)
0-2	324 (48.6)	54 (40.9)	16 (44.4)
Missing	1 (0.2)	—	—
Age at menarche, y	13 (12—14)		
≥11	600 (90.0)	113 (85.6)	27 (75.0)
<11	66 (9.9)	19 (14.4)	9 (25.0)
Missing	1 (0.1)	—	—
Parity[b]	2 (1—3)		
0	91 (13.6)	12 (9.1)	3 (8.3)
≥1	576 (86.4)	120 (90.9)	33 (91.7)
Lifetime oral contraceptive or other exogenous hormone use			
Yes	369 (55.3)	32 (24.2)	11 (30.6)
No	298 (44.7)	100 (75.8)	25 (69.4)
Alcohol use			
No	415 (62.2)	87 (65.9)	18 (50.0)
1-2 drinks	75 (11.2)	9 (6.8)	4 (11.1)
3-4 drinks	64 (9.6)	11 (8.3)	3 (8.3)
≥5 drinks	113 (16.9)	25 (18.9)	11 (30.6)
Cigarette smoking exposure[b]			
No	483 (72.41)	83 (62.9)	17 (47.2)
Yes	173 (25.94)	49 (37.1)	19 (52.8)
Missing	11 (1.65)	—	—

Calvet. Predictors of menopause in HIV-infected women. Am J Obstet Gynecol 2015. *(continued)*

TABLE 1
Characteristics of 667 participants followed at Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, 1996 through 2011 *(continued)*

Characteristic	Total (n = 667)	Natural menopausal women (n = 132)	Early natural menopausal women (n = 36)
Cigarette exposure in pack-y	9.5 (2.7–23.2)		
Never smoked	353 (52.9)	51 (38.6)	11 (30.6)
<10	151 (22.6)	30 (22.7)	10 (27.8)
10-19	58 (8.7)	16 (12.1)	3 (8.3)
≥20	90 (13.5)	34 (25.8)	12 (33.3)
Missing	15 (2.2)	1 (0.8)	—
Lifetime illicit drug use			
No	550 (82.5)	111 (84.1)	27 (75.0)
Yes	117 (17.5)	21 (15.9)	9 (25.0)
Lifetime cocaine use (intravenous or snorted)			
No	579 (86.8)	118 (89.4)	29 (80.6)
Yes	88 (13.2)	14 (10.6)	7 (19.4)
Body mass index, kg/m^2[b,c]			
Normal weight	324 (48.6)	74 (56.1)	21 (58.3)
Overweight/obese	247 (37.0)	46 (34.8)	10 (27.8)
Underweight	51 (7.6)	9 (6.8)	4 (11.1)
Missing	45 (6.8)	3 (2.3)	1 (2.8)
Type 2 diabetes			
No	589 (88.3)	108 (81.8)	29 (80.6)
Yes	78 (11.7)	24 (18.2)	7 (19.4)
Chronic hepatitis C virus[b]			
No	633 (94.9)	116 (87.9)	31 (86.1)
Yes	34 (5.1)	16 (12.1)	5 (13.9)
Hypothyroidism[b]			
No	654 (98.1)	129 (97.7)	35 (97.2)
Yes	13 (1.9)	3 (2.3)	1 (2.8)
CD4 count nadir, cells/mm^3	182 (74–278)		
≥350	94 (14.1)	12 (9.1)	3 (8.3)
200-349	213 (31.9)	34 (25.8)	7 (19.4)
100-199	155 (23.2)	28 (21.2)	10 (27.9)
50-99	81 (12.1)	23 (17.4)	4 (11.1)
<50	123 (18.4)	35 (26.5)	12 (33.3)
Missing	1 (0.1)	—	—

Calvet. Predictors of menopause in HIV-infected women. Am J Obstet Gynecol 2015. *(continued)*

(eg, when removed, a change ≥10% in the hazard ratio [HR] of any other variable of the model was observed) remained in the final model.[40] Proportionality of risks was tested using Schoenfeld residuals analysis.[41]

Software (R, version 3.0.2; R Foundation for Statistical Computing, Vienna, Austria) was used in all analyses.

Ethical statement

The study protocol was reviewed and approved by IPEC, Oswaldo Cruz Foundation (CAE 020/2001) Ethics Committee. Written informed consent was obtained from all the women.

RESULTS

Sample characteristics

In all, 667 women were followed for a total of 3814 person-years with a median follow-up of 5.0 years (IQR, 2.7–8.3). Of the 667 women, 142 (21.4%) were censored from the study during the observational period for the following reasons: 41 (6.1%) died, 23 (3.4%) had surgically induced menopause, 5 (0.7%) had chemotherapy or radiation-induced menopause, 4 (0.6%) were transferred to another facility, and 69 (10.3%) missed their scheduled follow-up gynecological visit for >1 year.

The characteristics of the study population are shown in Table 1. The median baseline age was 34.9 years (IQR, 30.9–40.5). The majority of women were nonwhite (60.4%) with up to 8 years of schooling (56.2%) and a family income ≤5 Brazilian minimum wages (80.8%). The median age at menarche was 13 years (IQR, 12–14), and 60.9% of the women were multiparous. Forty percent (n = 314) of women reported a lifetime exposure to cigarette smoking, but only 26% (n = 173) remained under exposure to cigarette smoking during the study observation period. Overall, women who had quit smoking did so for a median of 11.7 years (IQR, 5.5–19.0) prior to natural menopause or exclusion from the study. Among the 173 women exposed to cigarette smoking during the observational period, 20.2% (n = 35) reported smoking cessation; of these, 20% experienced natural menopause, and the median time from smoking

TABLE 1
Characteristics of 667 participants followed at Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, 1996 through 2011 *(continued)*

Characteristic	Total (n = 667)	Natural menopausal women (n = 132)	Early natural menopausal women (n = 36)
CD4 count, cells/mm^3[b,c]			
≥350	334 (50.1)	52 (39.4)	12 (33.3)
200-349	153 (22.9)	31 (23.5)	11 (30.6)
100-199	81 (12.1)	24 (18.2)	7 (19.4)
50-99	33 (5.0)	12 (9.1)	3 (8.3)
<50	28 (4.2)	8 (6.0)	2 (5.6)
Missing	38 (5.7)	5 (3.8)	1 (2.8)
AIDS-defining illnesses			
No	373 (55.9)	56 (42.4)	12 (33.3)
Yes	294 (44.1)	76 (57.6)	24 (66.7)
Combination antiretroviral therapy exposure			
No	77 (11.5)	14 (10.6)	3 (8.3)
Yes	590 (88.5)	118 (89.4)	33 (91.7)

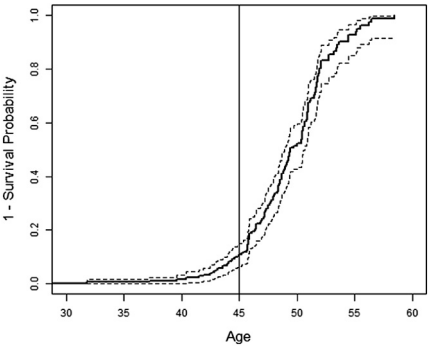
Data are presented as n (%) and median (interquartile range) values.

AIDS, acquired immune deficiency syndrome.

[a] In Brazilian minimum wages; [b] Frequencies presented for baseline but as time-dependent covariate; [c] Baseline body mass index and CD4 cell counts were defined as values obtained within 6 months (before or after) of enrollment.

Calvet. Predictors of menopause in HIV-infected women. Am J Obstet Gynecol 2015.

FIGURE 2
Reverse survival curve for natural menopause



Kaplan-Meier plot of age of natural menopause (*solid line*) with upper-lower interquartile range (*dashed line*), Instituto de Pesquisa Clínica Evandro Chagas, Rio de Janeiro, 1996 through 2011.

Calvet. Predictors of menopause in HIV-infected women. Am J Obstet Gynecol 2015.

cessation until the onset of natural menopause was 11.5 years (IQR, 5.8−18.6).

The median nadir CD4 count was 182 cells/mm^3 (IQR, 74−278), and 53.7% of women had a nadir CD4 count <200 cells/mm^3. Lifetime cART exposure was reported by 88.5% of women for a median time of 4.9 years (IQR, 2.4−9.0).

Age at natural menopause and its predictors

Natural menopause was observed in 132 of 667 women, corresponding to an incidence of 3.46 per 100 person-years (95% confidence interval [CI], 2.90−4.09). The probability of reaching menopause at age ≤50 years was .5 (95% CI, 0.40−0.57) (Figure 2). The median age at natural menopause was 48 years (IQR, 45−50).

The results from univariate and multivariate analysis for age at natural menopause are presented in Table 2. As cigarette smoking exposure and cigarette exposure in pack-years covariates were collinear, the former was chosen for multivariate analysis. Collinearity was observed between the time-dependent CD4 cell count and CD4 cell count nadir covariates, and the former was chosen for multivariate analysis.

Early menarche (HR, 2.03; 95% CI, 1.23−3.37), cigarette smoking exposure (HR, 1.59; 95% CI, 1.08−2.33), chronic HCV (HR, 2.53; 95% CI, 1.27−5.07), and a CD4 count <50 cells/mm^3 (HR, 3.07; 95% CI, 1.07−8.80) remained significantly associated with age at natural menopause in the final multivariate model.

Predictors of early age at natural menopause

In all, 608 women were evaluated for the outcome of early age at natural menopause and were followed up for a total of 3299 person-years with a median follow-up of 4.6 years (IQR, 2.5−7.7). Of these, 112 (18.4%) were censored from the study for the following reasons: 33 (5.4%) died, 15 (2.5%) had surgically induced menopause, 4 (0.7%) had chemotherapy or radiation-induced menopause, 4 (0.7%) transferred out of the study, and 56 (9.2%) missed their scheduled follow-up gynecological visit for >1 year.

Early natural menopause was observed in 36 women, with an incidence of 1.09 (95% CI, 0.77−1.49) per 100 person-years. The probability of reaching menopause at age ≤45 years was .1 (95% CI, 0.06−0.15) (Figure 2). Only 3 women experienced premature menopause.

The results from univariate and multivariate analyses for early age at natural menopause are presented in Table 3. The same collinearity profile as that for age at natural menopause outcome was observed. Cigarette smoking exposure and time-dependent CD4 cell count covariates were entered into the initial multivariate model.

The magnitudes of the effects of early menarche (HR, 2.70; 95% CI, 1.23−5.94), cigarette smoking exposure

TABLE 2
Unadjusted and adjusted hazard ratios for age at natural menopause from Cox proportional hazards modeling, 1996 through 2011 (n = 667)

	Unadjusted analysis			Adjusted analysis		
Characteristic	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Race/ethnicity						
White	1					
Nonwhite	0.71	0.50–1.01	.053			
Schooling, y						
>11	1					
>8-11	1.21	0.62–2.35	.578			
≤8	1.34	0.71–2.52	.373			
Monthly family income[a,b]						
>5	1					
2-5	1.34	0.85–2.10	.205			
0-2	1.09	0.71–1.68	.684			
Age at menarche, y[b]						
≥11	1			1		
<11	1.98	1.20–3.24	.007	2.03	1.23–3.37	.006
Parity[b]						
0	1			1		
≥1	0.60	0.32–1.13	.116	0.55	0.29–1.05	.071
Lifetime oral contraceptive or other exogenous hormone use						
Yes	1			1		
No	1.41	0.94–2.12	.102	1.44	0.95–2.18	.085
Alcohol use						
No	1					
1-2 drinks	0.73	0.37–1.46	.377			
3-4 drinks	0.97	0.52–1.83	.931			
≥5 drinks	0.81	0.52–1.27	.355			
Cigarette smoking exposure[b,c]						
No	1			1		
Yes	1.62	1.12–2.36	.011	1.59	1.08–2.33	.018
Lifetime cocaine use (intravenous or snorted)						
No	1					
Yes	0.77	0.44–1.34	.348			
Body mass index, kg/m^2[b,c]						
Normal weight	1			1		
Overweight/obese	0.68	0.48–0.97	.034	0.74	0.52–1.07	.111
Underweight	0.73	0.26–2.00	.538	0.75	0.27–2.07	.573

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TABLE 2
Unadjusted and adjusted hazard ratios for age at natural menopause from Cox proportional hazards modeling, 1996 through 2011 (n = 667) *(continued)*

Characteristic	Unadjusted analysis			Adjusted analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Type 2 diabetes						
No	1					
Yes	0.80	0.50–1.27	.339			
Chronic hepatitis C virus[b]						
No	1			1		
Yes	2.02	1.06–3.88	.034	2.53	1.27–5.07	.009
Hypothyroidism[b]						
No	1					
Yes	0.37	0.05–2.80	.336			
CD4 count, cells/mm^3[b,c]						
≥350	1			1		
200-349	1.07	0.67–1.72	.766	1.02	0.63–1.65	.934
100-199	1.07	0.48–2.36	.873	0.92	0.41–2.10	.849
50-99	1.06	0.34–3.37	.918	0.82	0.25–2.67	.741
<50	3.47	1.24–9.71	.018	3.07	1.07–8.80	.037
AIDS-defining illnesses						
No	1			1		
Yes	1.51	1.07–2.15	.020	1.40	0.97–2.04	.075
Combination antiretroviral therapy exposure						
No	1					
Yes	0.74	0.42–1.30	.291			

AIDS, acquired immune deficiency syndrome; *CI*, confidence interval; *HR*, hazard ratio.

[a] In Brazilian minimum wages; [b] Missing data—monthly family income: n = 1, menarche: n = 1, cigarette smoking: n = 11, body mass index: n = 18, CD4 cell count: n = 1; [c] Time-dependent variable measured during follow-up.

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(HR, 3.00; 95% CI, 1.39–6.45), chronic HCV (HR, 6.26; 95% CI, 2.12–18.52), and time-dependent CD4 count <50 cells/mm^3 (HR, 6.64; 95% CI, 1.91–23.20) were much higher and significantly associated with early age at natural menopause in the final multivariate model.

Race/ethnicity, schooling, monthly family income, parity, oral contraceptive and or other exogenous hormone use, alcohol and cocaine use, BMI, type 2 diabetes, hypothyroidism, and cART use were not found as significant predictors of earlier age at natural menopause and early natural menopause. The proportionality of risks was verified in both the age at natural menopause and the early age at natural menopause models.

Comment

The median age at natural menopause in the present study falls within the range of values reported in other international studies of HIV-infected women[17-20] and is similar to the median age reported in a prior Brazilian study.[16] Results from the present study are not comparable with those described in a Brazilian population-based study,[15] which described the mean age at menopause of 51.2 years, mainly due to different inclusion criteria regarding age of women in both studies. Therefore, it cannot be assumed that the age at natural menopause in the cohort of HIV-positive women is lower than the general Brazilian population.

Our study identified early menarche, cigarette smoking exposure during the observational period, chronic HCV coinfection, and severe immunosuppression as predictors of an earlier age at natural menopause. We also found that 27% of women reached natural

TABLE 3
Unadjusted and adjusted hazard ratios for early (≤45 years) natural menopause from Cox proportional hazards modeling, 1996 through 2011 (n = 608)

Characteristic	Unadjusted analysis			Adjusted analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Race/ethnicity						
White	1					
Nonwhite	0.59	0.30–1.13	.113			
Schooling, y						
>11	1					
>8-11	2.57	0.58–11.4	.214			
≤8	2.55	0.60–10.87	.207			
Monthly family income[a,b]						
>5	1					
2-5	1.03	0.43–2.49	.943			
0-2	1.17	0.52–2.65	.707			
Age at menarche, y[b]						
≥11	1			1		
<11	3.07	1.44–6.54	.004	2.70	1.23–5.94	.014
Parity[b]						
0	1					
≥1	1.32	0.40–4.30	.648			
Lifetime oral contraceptive or other exogenous hormone use						
Yes	1					
No	1.80	0.89–3.67	.104			
Alcohol use						
No	1			1		
1-2 drinks	1.33	0.45–3.92	.611	1.18	0.38–3.64	.779
3-4 drinks	1.11	0.33–3.76	.873	0.65	0.18–2.41	.523
≥5 drinks	2.13	1.01–4.52	.048	1.32	0.55–3.16	.534
Cigarette smoking exposure[b,c]						
No	1			1		
Yes	4.08	2.11–7.89	< .001	3.00	1.39–6.45	.005
Lifetime cocaine use (intravenous or snorted)						
No	1					
Yes	1.91	0.84–4.36	.125			
Body mass index, kg/m^2[b,c]						
Normal weight	1			1		
Overweight/obese	0.45	0.23–0.91	.027	0.53	0.25–1.10	.086
Underweight	0.49	0.07–3.63	.485	0.32	0.04–2.53	.280

Calvet. Predictors of menopause in HIV-infected women. Am J Obstet Gynecol 2015. *(continued)*

TABLE 3
Unadjusted and adjusted hazard ratios for early (≤45 years) natural menopause from Cox proportional hazards modeling, 1996 through 2011 (n = 608) *(continued)*

Characteristic	Unadjusted analysis			Adjusted analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Type 2 diabetes						
No	1					
Yes	1.08	0.47–2.47	.853			
Chronic hepatitis C virus[b]						
No	1			1		
Yes	5.39	2.09–13.89	< .001	6.26	2.12–18.51	.001
CD4 count, cells/mm^3[b,c]						
≥350	1			1		
200-349	1.14	0.46–2.85	.773	1.06	0.41–2.74	.90
100-199	1.99	0.68–5.83	.212	1.31	0.41–4.20	.647
50-99	2.60	0.61–11.15	.199	1.18	0.23–5.94	.842
<50	8.24	2.77–24.48	< .001	6.64	1.91–23.16	.003
AIDS-defining illnesses						
No	1			1		
Yes	2.38	1.19–4.75	.014	1.49	0.67–3.33	.327
Combination antiretroviral therapy exposure						
No	1					
Yes	0.86	0.26–2.79	.795			

AIDS, acquired immune deficiency syndrome; *CI*, confidence interval; *HR*, hazard ratio.

[a] In Brazilian minimum wages; [b] Missing data—monthly family income: n = 1, menarche: n = 1, cigarette smoking: n = 11, body mass index: n = 18, CD4 cell count: n = 1; [c] Time-dependent variable measured during follow-up.

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menopause at the age of ≤45 years, falling into the definition of early menopause. Similar high proportions of early menopause were observed by Fantry et al[42] (20%) and de Pommerol et al[18] (22%), although these studies included a smaller sample size. Additionally, the rate of premature menopause was lower in our study (2.3%) compared to other studies conducted in HIV-infected women, in which high rates of premature menopause were observed.[18,20,42,43]

In the analysis of early age at natural menopause, we only observed women who were at risk for early natural menopause by restricting the analysis to women <45 years of age. Of note, we found that although the same risk factors were observed for both outcomes, their impact was much higher when we studied the early natural menopause outcome.

Reproductive factors, such as early age at menarche and increased parity, may be associated with age at menopause, as the occurrence of fewer menstrual cycles prevents oocyte depletion and leads to a delay in the cessation of ovarian function. In our study, early menarche (<11 years) was significantly associated with both age at natural menopause and early age at natural menopause, and this is in agreement with studies performed in the general population.[44,45] However, in the present study, parity was not a predictor of an earlier age of natural menopause. Schoenbaum et al[20] found that lower parity was associated with an increased likelihood of earlier onset of menopause in HIV-positive women, although this result has not been confirmed by other research.[18,19]

Current cigarette smoking was related to both age at natural menopause and early age at natural menopause. Indeed, smoking is known as one of the factors most consistently associated with age at natural menopause.[46,47] Studies from the general population suggest an acceleration of menopause of up to 2 years for women who smoke compared to nonsmokers,[48,49] and other studies suggest that substances present in cigarettes might be associated with irreversible damage of the ovarian follicles and impaired liver estrogen metabolism.[50] Interestingly, women who stop smoking many years before menopause have been shown to reach menopause at ages

more similar to those who have never smoked.[9] Therefore, it seems that current smoking near the time of menopause, rather than the duration (length of time of use of tobacco) or intensity (pack-years of tobacco intake throughout life) of smoking, is the main risk factor related to early menopause.[51,52]

Higher BMI was not a predictor of later age at natural menopause in our study, and this is consistent with the majority of other studies, including those evaluating HIV-infected women.[19,20,48,53] Greater weight gain from 20-40 years of age has been shown to be associated with later menopause, suggesting that menopausal age might be mediated by weight changes over time,[54] although this finding has not been consistent among studies.[55]

HCV coinfection was significantly associated with age at natural menopause and with early age at natural menopause, and this finding is in agreement with data from women in the general population.[56] Amenorrhea is the most common menstrual-related finding in women with advanced liver disease, and alterations in hormone metabolism and/or dysfunction of the hypothalamic-pituitary axis[57-59] may be the basis for the early onset of menopause in women with chronic HCV infection, but these hypotheses merit further investigation. Moreover, postmenopausal HCV-infected women receiving hormone therapy demonstrate lower-stage fibrosis, similar to premenopausal women,[60,61] and the severity of fibrosis worsens in parallel with progressive estrogen deprivation and the decrease in the estradiol/testosterone ratio.[62] Reproductive status was also shown to be an important predictor in the response to pegylated interferon/ribavirin antiviral therapy.[63] These data reinforce the potential antifibrogenic protective role of estrogens[64,65] and highlight the clinical impact of earlier age at menopause in chronic HCV-infected women. Other chronic diseases, such as type 2 diabetes[66] and hypothyroidism,[67] have also been associated with earlier menopause, but we did not observe such associations in our study.

Severe immunosuppression was associated with both study outcomes. Prior studies have shown that HIV-associated factors such as CD4 cell counts <200 cells/mm^3,[18,20,43] and CDC classification B/C[19] or C[43] were associated with an increased risk of earlier menopause. These results enforce the critical importance of earlier HIV diagnosis with prompt cART initiation in mediating this sex-specific effect of advanced immunodeficiency.

Our study had several strengths. For instance, the longitudinal design and large urban cohort of HIV-infected women with prospective measurements of the FMP reduced the chance of recall bias that is sometimes observed in retrospective studies, which is important because the reliability of the final estimate is determined by the length of time elapsed since the FMP. The cutoff age of 30 years at the initiation of follow-up allowed for the evaluation of women who developed the outcome of interest earlier without excluding them from the analyses, which might have overestimated the median age at menopause.

One of the limitations of this study was that no hormonal tests were performed to confirm menopausal status. To minimize this limitation, all women considered as postmenopausal in our study were followed up after the end of our study, with a median observation time of 2.5 years (IQR, 1.3–5.4 years) from the FMP until the last follow-up gynecological visit (data not shown), thus confirming their menopausal status.

As there are scarce data on natural menopause among HIV-infected women in the literature, even in the absence of a matched group of HIV-negative women, the results of the present study estimated median age at natural menopause (48 years; IQR, 45–50 years) in a large cohort of HIV-infected women, as well described the predictors of early natural menopause among these women, which may contribute to further research in this field.

In conclusion, the median age at natural menopause among HIV-infected women was similar to that of other international studies of HIV-infected women. Early natural menopause was frequent in our cohort (27%), and early menarche, severe immunodeficiency, chronic HCV coinfection, and cigarette smoking exposure were significantly associated with age at natural menopause and with early age at natural menopause. Race/ethnicity, schooling, monthly family income, parity, oral contraceptive and or other exogenous hormone use, alcohol and cocaine use, BMI, type 2 diabetes, hypothyroidism, and cART use were not found as significant predictors of earlier age at natural menopause and early natural menopause. These results have clinical and public health implications, as an earlier age of menopause has been associated with increased morbidity and mortality. Moreover, HIV-infected postmenopausal women represent an expanding group, and a better understanding of aging in these women is of paramount importance to determine a more appropriate disease-management approach during this period of life. ■

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