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Authors

Scherzer, Rebecca
Greenblatt, Ruth M
Merhi, Zaher O
et al.

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Use of antimüllerian hormone to predict the menopausal transition in HIV-infected women

Rebecca Scherzer, PhD, **Ruth M. Greenblatt, MD**, **Zaher O. Merhi, MD**, **Seble Kassaye, MD, MS**, **Geralyn Lambert-Messerlian, PhD**, **Pauline M. Maki, PhD**, **Kerry Murphy, MD**, **Roksana Karim, PhD**, and **Peter Bacchetti, PhD**

Departments of Medicine (Drs Scherzer and Greenblatt), Clinical Pharmacy (Dr Greenblatt), and Epidemiology and Biostatistics (Drs Greenblatt and Bacchetti), University of California, San Francisco, and the San Francisco Department of Veterans Affairs Medical Center (Dr Scherzer), San Francisco, CA; Department of Obstetrics and Gynecology, Division of Reproductive Biology, New York University School of Medicine, New York, NY (Dr Merhi); Department of Infectious Diseases, Georgetown University Medical Center, Washington, DC (Dr Kassaye); Department of Pathology and Laboratory Medicine, Women and Infants Hospital, Providence, RI (Dr Lambert-Messerlian); Departments of Psychiatry and Psychology, College of Medicine, University of Illinois at Chicago, Chicago, IL (Dr Maki); Department of Medicine, Albert Einstein College of Medicine, Bronx, NY (Dr Murphy); and University of Southern California, Los Angeles, CA (Dr Karim)

Abstract

BACKGROUND—HIV infection has been associated with early menopausal onset, which may have adverse long-term health consequences. Antimüllerian hormone, a biomarker of ovarian reserve and gonadal aging, is reduced in HIV-infected women.

OBJECTIVE—We sought to assess the relationship of antimüllerian hormone to age of menopause onset in HIV-infected women.

STUDY DESIGN—We used antimüllerian hormone levels measured in plasma in 2461 HIV-infected participants from the Women's Interagency HIV Study to model the age at final menstrual period. Multivariable normal mixture models for censored data were used to identify factors associated with age at final menstrual period.

RESULTS—Higher antimüllerian hormone at age 40 years was associated with later age at final menstrual period, even after multivariable adjustment for smoking, CD4 cell count, plasma HIV RNA, hepatitis C infection, and history of clinical AIDS. Each doubling of antimüllerian hormone was associated with a 1.5-year increase in the age at final menstrual period. Median age at final menstrual period ranged from 45 years for those in the 10th percentile of antimüllerian hormone to 52 years for those in the 90th percentile. Other factors independently associated with earlier age at final menstrual period included smoking, hepatitis C infection, higher HIV RNA levels, and history of clinical AIDS.

Corresponding author: Ruth M. Greenblatt, MD. ruth.greenblatt@ucsf.edu.

The remaining authors report no conflict of interest.

CONCLUSION—Antimüllerian hormone is highly predictive of age at final menstrual period in HIV-infected women. Measuring antimüllerian hormone in HIV-infected women may enable clinicians to predict risk of early menopause, and potentially implement individualized treatment plans to prevent menopause-related comorbidities and to aid in interpretation of symptoms.

Keywords

AIDS; antimüllerian hormone; hepatitis C virus infection; HIV; menopause; ovarian reserve; viremia

Introduction

Even among recipients of potent antiretroviral therapy, HIV infection has been reported to be associated with early onset of menopause.[1–3] Women represent about 25% of HIV-infected persons in the United States[4] and over half of all HIV-infected persons globally.[5] Early menopause is a risk factor for bone loss, cardiovascular disease (CVD), and neurological disease.[6–8] This is particularly concerning in the setting of HIV infection, since HIV infection itself has been associated with increased risk of CVD, low bone mass, and other comorbidities. Additionally, menopause is associated with vasomotor symptoms such as hot flashes, night sweats, and sleep disruption that also occur with the progression of HIV illnesses or the adverse effects of antiretroviral medications.[1]

Ovarian production of sex steroids (ie, progesterone, estradiol, and testosterone) contributes to sex differences in immune responses and CVD.[9,10] While bone demineralization increases with the loss of ovarian steroids after menopause, the impact of menopause on the persistence of other sex differences is unknown, including differences in HIV disease progression and AIDS-defining diseases. In HIV-infected women, menopause affects immune function[11] and thus disease progression, leading to lower CD4 cell counts.[12,13] Menopause also adversely influences the outcome of antiviral therapy for hepatitis C virus (HCV) infection.[14]

We recently reported that plasma levels of antimüllerian hormone (AMH), a biomarker of ovarian reserve and gonadal aging, are lower in HIV-infected women.[15] The relationship of levels of AMH to age of menopause onset has been studied in the general population,[16–19] but is unknown in HIV-infected women. Likewise, factors associated with age at menopause have been well characterized in the general population,[20,21] but few prospective studies in HIV-infected women have been conducted.

The objective of this study was to use levels of AMH measured in plasma to model the age of final menstrual period (FMP) in 2461 ethnically diverse HIV-infected participants from the Women's Interagency HIV Study (WIHS). We also sought to identify other factors associated with age at FMP in HIV-infected women, including lifestyle factors, lymphocyte variables, parity, gravidity, use of sex steroids, age at menarche, and HIV-related variables.

Materials and Methods

Study population

The WIHS is a longitudinal observational cohort study of HIV infection and related conditions in women.[22] Participants are interviewed and examined every 6 months. Women who contributed data to this report were enrolled in the first or second expansions of WIHS. In brief, 3766 women (2791 HIV-infected and 975 HIV-uninfected) were enrolled in either 1994 through 1995 (n = 2623, early cohort) or 2001 through 2002 (n = 1143, late cohort) from 6 US sites (Bronx/Manhattan, NY; Brooklyn, NY; Chicago, IL; Los Angeles, CA; San Francisco, CA; and Washington, DC). Enrollment in the early cohort occurred prior to the broad availability of potent antiretroviral regimens, and thus is a rough indicator of longer duration of untreated HIV infection. HIV-infected WIHS participants are representative of HIV-infected women in the United States, based on contemporaneous national and local surveillance reports regarding demographics and risk factors for prevalent HIV cases among women.[23–25]

For this analysis, participants with a history of cancer chemotherapy were excluded, because previous studies have shown that such treatment can result in a rapid decline in AMH values.[26] There were no exclusions for menstrual characteristics such as cycle length or irregularity. The median number of AMH measurements for each participant was 3 (interquartile range 2–5), and median follow-up between first and last AMH measurements was 7 years (interquartile range 5–11) for those with at least 2 measures. Written informed consent was provided by all participants after approval of the human subjects protocols by internal review committees at each affiliated institution.

AMH assay

AMH levels were determined using a commercially available enzyme-linked immunosorbent assay (Gen II; Beckman Coulter Inc, Chaska, MN). Plasma samples were frozen at −80°C and not thawed prior to testing, which was conducted blind to HIV status. Interassay coefficients of variations were 8.2% at 2.8 ng/mL and 9.4% at 8.5 ng/mL. The lower limit of detection was 0.08 ng/mL.

The primary predictor in this study was AMH level at age 40 years, which was estimated for all women using the fitted random intercept from a left-censored linear mixed effects regression model of log-transformed AMH, via previously published methods.[15] Of the 2740 HIV-positive participants with measured AMH, 32% had values measured within 1 year of age 40 years and 71% had AMH measured within 5 years of age 40 years. Examination of model fit for the left-censored random effects model showed a substantial proportion of outliers, where accurate estimates of AMH at age 40 years could not be obtained. Women who were older and had AMH value below assay detection at the time of WIHS enrollment tended to have larger SE for estimated AMH at age 40 years. We therefore excluded participants with SE >2 (9% of the total). We also conducted sensitivity analyses to address uncertainty in the estimation of AMH at age 40 years. These analyses included use of an uncertainty weight to downweight observations with large SE (calculated as $1/SE^2$, where SE = the SE of estimated AMH at age 40 years), multiple imputation (using the SAS

[SAS Institute Inc, Cary, NC] MMI_IMPUTE macro for multilevel data[27]), and restriction of the cohort to those with AMH measured near age 40 years (defined as ±1 year and as ±5 years).

Other measurements

Study interviews assessed regularity of menstrual periods, obstetrical history, history of gynecological surgery and medical conditions, use of tobacco and illicit drugs, and use of exogenous steroids and other medications. HIV serology was performed at baseline and prospectively in women with negative results. Quantification of HIV RNA copy numbers (viral load) was performed on plasma, using NucliSens (bioMérieux, Inc, Durham, NC), NASBA (nucleic acid sequence based amplification), Taqman (Thermo Fisher Scientific Inc, North Waltham, MA), and Roche Amplicor (Roche Molecular Systems Inc, Pleasanton, CA) assays with limits of detection ranging from 20–300 copies/mL, depending on testing date. Lymphocyte subsets (including determination of $CD3^+$ $CD4^+$ and $CD3^+$ $CD8^+$ cell counts) were measured in whole blood semiannually using laboratories that participate in the National Institute of Allergy and Infectious Diseases Division of AIDS Virology and Immunology Laboratory Quality Assurance Programs. This analysis used the $CD4^+$ (T-helper cell) counts measured at the time of the WIHS visit closest to age 40 years and the nadir count (lowest $CD4^+$ T-cell count measured prior to age 40 years). HCV infection was identified by second-generation or third-generation enzyme-linked immunoassay serology at WIHS entry. HCV RNA testing methods included the Roche COBAS AMPLICOR HCV MONITOR test (v2.0/Kovacs, w01043; Roche Molecular Systems) and the TAQMAN test (w07007 and w07034; Thermo Fisher Scientific Inc).

Outcome

The primary outcome of this study was age at FMP, defined using self-reports provided at study visits. The occurrence of FMP was defined as self-reported menstrual period followed by at least 2 consecutive semiannual WIHS visits at which no interval menses was reported. Women reporting recurrence of menses after amenorrhea were not considered to have FMP. Additionally, women who reported amenorrhea during or immediately following pregnancy were not considered to have FMP. Within this cohort, age at FMP could be left censored (occurring prior to the first WIHS visit), interval censored/observed (recorded during WIHS), or right censored (had not yet occurred at last WIHS visit).

Covariates

For this analysis, covariates were selected using the individual participant's WIHS visit that occurred closest to age 40 years, to correspond to the level of AMH measured at that age. Candidate covariates included demographics (age, race/ethnicity), WIHS enrollment cohort (early vs late), lifestyle factors (smoking and illicit drug use), body mass index (BMI), waist circumference, fertility and menstrual-related factors (parity, gravidity, use of sex steroids, age at menarche), lymphocyte variables (current and nadir levels of $CD4^+$, $CD8^+$, total lymphocytes, and white blood cell [WBC] counts), and HIV-related factors (use of antiretroviral medications, number of HIV RNA copies in plasma [viral load], history of clinical AIDS, hepatitis C serology status, and history of weight loss). Multiple imputation using the Markov chain Monte Carlo method for arbitrary missing multivariate normal data

was used to impute missing covariates, with 10 imputations to ensure ~95% relative efficiency.[28] The percentage of missing observations for each covariate ranged from <1–11%. Missing values were imputed before fitting the FMP prediction model.

Statistical methods

We compared demographic and clinical characteristics of HIV-infected women by tertile of AMH measured at age 40 years using the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables, because several variables were not normally distributed.

We constructed normal mixture models using SAS NLMIXED (SAS Institute Inc, Cary NC) to account for censoring in the outcome while allowing estimates of age at FMP in years, following a model developed by Boldsen and Jeune.[29] This method allowed us to accommodate a mixture of early and late normal distributions. As a sensitivity analysis, we tested models that included a mixture of 3 normal distributions (early, mid, and late) (Supplemental Table 1); model fit was similar and predictions were virtually identical to the 2-component model.

To ensure that the association of AMH with FMP was not distorted by confounders, we constructed multivariable models, adjusting for candidate covariates as listed above, using stepwise backward selection with a significance level of $\alpha = 0.05$ to remove candidate covariates. As an alternative model building approach, we used Bayesian model averaging, retaining predictors with posterior probabilities >35%.[30] The 2 approaches selected the same variables.

We estimated percentiles of age at FMP using the FROOT function in SAS IML (SAS Institute Inc, Cary NC) by solving for *age* in the equation:

$$(1-\pi_{early}) \bullet \Phi\left(\frac{age-\mu_{late}}{SD_{late}}\right) + \pi_{early} \bullet \Phi\left(\frac{age-\mu_{early}}{SD_{early}}\right) - p = 0,$$

where Φ is the standard normal cumulative distribution function, π_{early} denotes the probability of being in the early group, μ and SD denote the mean and SD for the early or late group, and p is the percentile of interest (eg, $P = .05$ for the 5th percentile).

Bayesian model averaging was conducted using the Bayesian model averaging package for R statistical computing language (R Development Core Team, Vienna, Austria). All other analyses were conducted using the SAS system, Version 9.4.

Results

Cohort characteristics

We first compared demographic and clinical characteristics of the 2461 HIV-infected participants by tertile of AMH estimated at age 40 years (Table 1). HIV-infected women with lower estimated AMH at age 40 years were more often smokers and current users of

heroin and/or crack/cocaine, relative to those with higher AMH. HIV-positive women in the lowest AMH tertile also had lower BMI and greater weight loss relative to those with higher AMH. Participants with lower AMH at age 40 years were also more likely to have a history of clinical AIDS, coinfection with hepatitis C, detectable viral load, and lower lymphocyte counts (both current and nadir) and current and total WBC counts.

Association of AMH and other factors with age at FMP

We next examined unadjusted associations of AMH and other factors with age at FMP (Table 2). In unadjusted analysis, estimated AMH at age 40 years was positively associated with age at FMP, meaning that those with higher AMH levels had later ages at FMP. Each doubling of AMH was associated with a 1.5-year increase in the age at FMP (95% confidence interval [CI], 1.4–1.7; $P < .0001$). Factors associated with an earlier age at FMP included current smoking, current illicit drug use, lower BMI, history of weight loss or clinical AIDS, higher HIV viral load, serologic evidence of hepatitis C infection, and enrollment in the early cohort. Factors associated with a later age at FMP included greater CD4, CD8, total lymphocytes, and WBC counts.

After multivariable adjustment for lifestyle factors and HIV-related factors, higher AMH at age 40 years remained associated with a 1.5-year increase in the age at FMP, for every doubling in AMH (95% CI, 1.4–1.6; $P < .0001$) (Table 3). In an alternative model that replaced continuous AMH measurements with tertile categories, being in the highest tertile of AMH at age 40 years (>2.1 ng/mL) was associated with a 5.7-year greater age at FMP (95% CI, 5.1–6.4; $P < .0001$) relative to the lowest tertile (<0.7 ng/mL), while the middle tertile of AMH was associated with a 2.7-year increase (95% CI, 2.1–3.4; $P < .0001$). Other factors that were independently associated with earlier age at FMP included current smoking, hepatitis C serologic reactivity, and history of clinical AIDS. CD4 count and HIV RNA were individually associated with age at FMP, with similar model fit. However, both factors weakened when included simultaneously in the model (not shown).

We also constructed models to examine how the association of hepatitis C with earlier age at FMP varied by HCV RNA level. Among participants who were HCV seropositive who also had HCV RNA levels above the median (ie, >2.1 million IU), the estimated age at FMP occurred 1.1 year earlier on average (95% CI, −1.9 to −0.4; $P = .0020$) relative to those who were HCV seronegative. By contrast, among those with HCV RNA levels below the median, the estimated age at FMP occurred 0.3 years earlier on average (95% CI, −0.9 to 0.4; $P = .39$) relative to those who were HCV seronegative.

Because participants in the early cohort tended to have more severe HIV disease at the time of initiation of potent antiretroviral treatment, we also stratified our analysis by cohort (Supplemental Table 2). The association of estimated AMH at age 40 years with age at FMP appeared to be somewhat stronger in the early cohort (1.5 years per doubling of AMH; 95% CI, 1.4–1.7) compared with the later cohort (1.3 years per doubling of AMH; 95% CI, 1.0–1.6), but the test for interaction of cohort by AMH was not statistically significant ($P = .27$).

We conducted several sensitivity analyses to gauge the effect of uncertainty in the estimation of AMH at age 40 years (Supplemental Table 3). Our primary analysis excluded participants

with large SE of estimated AMH at age 40 years (9% of the total with SE >2). When we instead retained those with SE >2, higher AMH at age 40 years remained associated with a 1.5-year increase in the age at FMP, for every doubling in AMH (95% CI, 1.4–1.6; $P < .0001$). Other sensitivity analyses in which we used uncertainty weights, multiple imputation, or restricted the analysis to those with observed AMH near age 40 years yielded similar results (1.3- to 1.5-year increase in age at FMP per doubling of AMH, all $P < .0001$).

Finally, we estimated the age at FMP that would be associated with different levels of AMH (Figure) using our multivariable adjusted model. We divided women into percentiles of AMH level, shown on the x-axis. Women with a relatively low AMH level are included in the lower percentiles (solid gray circles) and women with a relatively high AMH level are included in the higher percentiles (open gray circles). For an HIV-infected woman with an AMH of 1.2 ng/mL (corresponding to the median level in our cohort), our model estimated that the median predicted age at FMP was 48.8 years. By contrast, at the 10th percentile of AMH (0.2 ng/mL), the median predicted age at FMP was 44.7 years. At the 90th percentile of AMH (5.5 ng/mL), the median predicted age at FMP was 52.1 years.

Comment

In this nationally representative cohort of HIV-infected women, we demonstrated that plasma AMH is highly predictive of age at FMP. AMH is an attractive marker in HIV-infected and other chronically ill women, whose menstrual patterns and symptoms may be an unreliable indicator of the menopausal transition. AMH level at age 40 years was strongly associated with age at FMP in HIV-infected women in our cohort, even after controlling for smoking and HIV-related factors. The median age at FMP ranged from 45–52 years (for those at the 10th and 90th percentiles of AMH, respectively). By comparison, a study of normo-ovulatory women reported a median predicted age at menopause ranging from 49–55 years (for those at the 10th and 90th percentiles of AMH, respectively),[18] consistent with a mean age of 51 years in the general population.[31]

Other factors that were independently associated with an earlier age at FMP included smoking, lower CD4 cell count or higher HIV RNA, hepatitis C coinfection (positive serology, and detectable HCV RNA in plasma), and history of clinical AIDS (AIDS defining opportunistic infection or malignancy). Consistent with our results, Calvet et al[1] found that smoking, HCV, and low CD4 cell counts were independently associated with earlier age at natural menopause in a prospective Brazilian cohort of 667 HIV-infected women. The Aquitaine cohort also found low CD4 count to be associated with early menopause, along with African origin and history of injection drug use.[2] A cross-sectional study of 559 impoverished women also found that HCV infection was independently associated with earlier menopause, after controlling for age, HIV status, drug use, parity, and physical activity.[32]

Recent studies report greater hepatic fibrosis severity in HCV-infected women following menopause[33] and in HCV-infected men and women with low estrogen receptor expression in the liver.[34] Whether this is due to the loss of estrogen’s protective effects or whether the HCV itself accelerates the onset of menopause is unclear. HCV infection is associated with

diminished follicular activation during assisted reproductive procedures,[35] possibly due to abnormal hormonal levels related to active HCV replication. Additionally, HCV infection may directly influence AMH production by altering granulosa cell function and increasing apoptosis.[36] Of note, we found a greater prevalence of HCV-coinfected women among those with the lowest AMH levels at age 40 years, suggesting that HCV-infected women had lower ovarian reserve.

In our study, low CD4 cell count and history of clinical AIDS were independent predictors of earlier age at FMP. We previously reported that higher CD4 cell counts were strongly associated with greater AMH levels in both HIV-infected and -uninfected women.[15] Among HIV-infected women who experienced antiretroviral-related CD4 count increases, there was an age-adjusted increase in AMH. These findings support the idea that CD4 cells may influence ovarian function, in particular granulosa cells that synthesize AMH.[15]

In unadjusted analysis, we found earlier age at FMP in participants enrolled in the WIHS early cohort as well as heroin/crack or cocaine users and those with a history of weight loss. We also found that HIV-related factors, including history of clinical AIDS and hepatitis C coinfection, appeared to have stronger effects in the early cohort than in women enrolled later, when potent HIV treatments were available. These findings may reflect the fact that participants in the early cohort were more likely to have a history of drug injection and to have clinical AIDS or symptomatic HIV infection than women enrolled later, who benefited from potent antiretroviral therapies. Even after receipt of potent therapy and recovery of CD4 cell counts in the peripheral blood, individuals with profound CD4 cell depletion and opportunistic infections may not recover full immune function. If ovarian function requires a fully robust immune system, women who have had advanced HIV disease may not regain the expected ovarian function possible for other women of similar age.

A major strength of this study is that it utilized an ethnically diverse sample that was not selected on the basis of infertility, menstrual pattern, or known fertility. Furthermore, we measured AMH at multiple visits over time in our participants, enabling us to estimate each participant’s level of AMH at age 40 years. Finally, AMH is more stable over the ovulatory cycle than other ovarian reserve biomarkers and can be measured accurately even in women with irregular cycles or amenorrhea induced by chronic illness, which improves its utility as a biomarker of ovarian reserve and gonadal aging.[37]

Our study had several limitations. Menstrual and medication histories were self-reported, and thus subject to recall error. HIV infection itself, particularly when disease is advanced, is associated with prolonged amenorrhea, and so we could not rule out the possibility that some participants who reported FMP may yet resume menses. The date of FMP was not observed during the study for all participants; however, we used normal mixture models appropriate for censored data to overcome this limitation. We did not have estrogen levels in this study, and so we cannot determine whether the association of AMH with FMP is driven more by the loss of estrogen’s protective effects or direct viral effects. Because AMH was estimated rather than measured precisely at age 40 years, we performed sensitivity analyses that addressed this uncertainty. The association with age at FMP was slightly attenuated when AMH was estimated using multiple imputation. We believe this result provides a

conservative assessment, because it does not reflect the expectation from errors-in-variable theory[38] that the true associations would be larger than our estimates. In addition, a newer, more sensitive AMH assay is now available that can measure picogram levels in serum. Use of this assay would allow for study of some women currently excluded for non-detectable AMH. Finally, there may have been incomplete or inadequate control for factors that may confound or explain the association between AMH and menopause.

In conclusion, we found that serum AMH is a strong and independent predictor of age at FMP in HIV-infected women. Individual prediction of age at menopause is highly relevant in the setting of HIV infection, given that over half of all HIV-infected persons living in the United States will be aged ≥50 years by the year 2020.[39] Measuring AMH in HIV-infected women may enable clinicians to predict risk of early menopause, and potentially implement individualized treatment plans to prevent and monitor menopause-related conditions such as bone loss and CVD risk. Additionally, smoking cessation may be of particular benefit in this group of women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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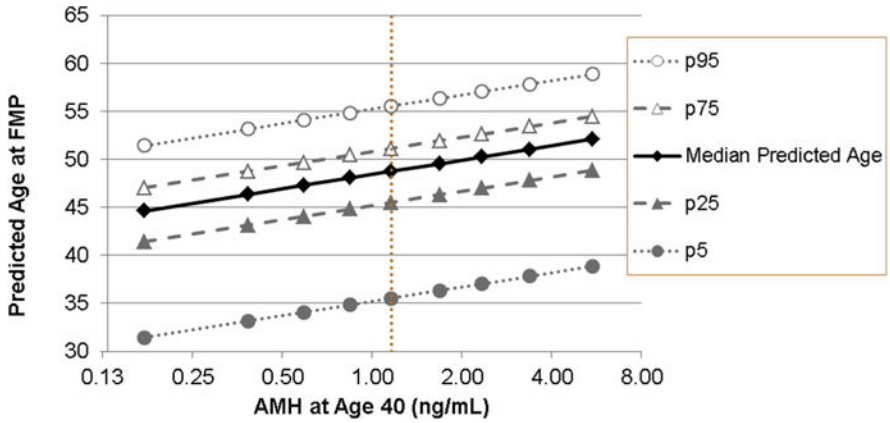

FIGURE. Predicted age at final menstrual period by AMH at age 40

Estimates are from multivariable-adjusted models provided in Table 3. Vertical reference line denotes median plasma antimüllerian hormone (AMH) level at age 40 years in this cohort.

FMP, final menstrual period.

TABLE 1

Summary of demographic and clinical characteristics for Women's Interagency HIV Study HIV-infected women at age 40 years, stratified by antimüllerian hormone tertile

Parameter	Estimated level of AMH at age 40 y			*P* value
	Tertile 1 N = 820	Tertile 2 N = 821	Tertile 3 N = 820	
Range of AMH at age 40 y	<0.7 ng/mL	0.7–2.1	>2.1 ng/mL	
Actual age, y[a]				
Median (IQR)	40 (38–40)	40 (38–46)	40 (40–40)	
Mean (SD)	39 ± 4	39 ±4	40 ±3	
Minimum, maximum	26, 46	26, 47	28, 56	
Race/ethnicity				
Black	485 (59%)	433 (53%)	442 (54%)	.085
Other	143 (17%)	156 (19%)	157 (19%)	
White	192 (23%)	232 (28%)	221 (27%)	
Smoking status				
Current	449 (55%)	403 (49%)	338 (41%)	<.0001
Past	153 (19%)	150 (18%)	196 (24%)	
Never	218 (27%)	268 (33%)	286 (35%)	
Early cohort	635 (77%)	569 (69%)	581 (71%)	.0005
Age at menarche, y	12 (11–13)	12 (11–13)	13 (11–14)	.19
Current heroin use	87 (11%)	67 (9%)	50 (6%)	.0057
Current crack/cocaine use	147 (19%)	125 (16%)	108 (14%)	.041
BMI, kg/m^2	26 (22–31)	27 (23–31)	27 (23–32)	<.0001
Waist circumference, cm	89 (80–101)	91 (81–102)	90 (81–101)	.32
History of weight loss	396 (48%)	310 (38%)	285 (35%)	<.0001
Parity	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.5)	.33
Ever pregnant	749 (91%)	759 (93%)	757 (92%)	.60
HAART use	273 (33%)	307 (38%)	355 (44%)	.0001
History of clinical AIDS	438 (53%)	332 (40%)	294 (36%)	<.0001
Hepatitis C	231 (32%)	213 (28%)	177 (24%)	.0032
Detectable HIVRNA	613 (81%)	566 (75%)	516 (69%)	<.0001
Current CD4, /mL	300 (109–505)	374 (195–588)	438 (267–635)	<.0001
Current CD8, /mL	709 (451–1004)	734 (531–1039)	814 (572–1084)	<.0001
Current total lymphocyte, /mL	149 (97–199)	162 (122–216)	179 (135–227)	<.0001
Total WBC, ×10^3/mL	14 (13–16)	15 (14–16)	15 (14–16)	<.0001
Nadir CD4, /mL	176 (38–343)	236 (102–367)	271 (136–407)	<.0001
Nadir CD8, /mL	521 (305–807)	547 (377–792)	581 (400–847)	.0002
Nadir total lymphocyte, /mL	115 (69–159)	126 (89–162)	133 (99–176)	<.0001
Nadir WBC, ×10^3/mL	13 (13–14)	14 (13–14)	14 (13–15)	<.0001

Data are presented as median (IQR) or numbers (percent) unless otherwise specified.

AMH, antimüllerian hormone; *BIC*, Bayesian information criterion; *BMI*, body mass index; *DF*, degrees of freedom; *HAART*, highly active antiretroviral therapy; *int*, intercept; *IQR*, interquartile range; *loc*, location; *NNRTI*, nucleoside reverse transcriptase inhibitor; *NRTI*, nucleoside reverse transcriptase inhibitor; *PI*, protease inhibitor; *prob*, probability; *Probt*, p value from t-test; *T lymph*, total lymphocyte count; *WBC*, white blood cell.

[a] At Women's Interagency HIV Study visit closest to age 40 y, as used to define other covariates.

TABLE 2

Unadjusted associations of antimüllerian hormone at age 40 years[a] and other parameters with age at final menstrual period

Parameter	Unadjusted Estimate in years (95% CI)	Parameter	Unadjusted Estimate in years (95% CI)
AMH at age 40 y, per doubling	1.53 (1.40–1.67) $P < .0001$	Early vs late cohort	−1.35 (−2.3 to −0.42) $P = .0046$
Black vs white	−0.74 (−1.59 to 0.099) $P = .084$	CD4 count, per doubling	0.65 (0.41–0.89) $P < .0001$
Other vs white	−0.72 (−1.74 to 0.30) $P = .17$	CD8 count, per doubling	0.42 (0.0066–0.84) $P = .046$
Current smoker	−2.9 (−3.8 to −2.1) $P < .0001$	T lymph, per doubling	1.19 (0.70–1.68) $P < .0001$
Past smoker	−1.13 (−2.2 to −0.11) $P = .030$	WBC total, doubling	2.7 (0.73–4.8) $P = .0077$
Current crack/cocaine use	−1.88 (−2.7 to −1.03) $P < .0001$	Nadir CD4, doubling	0.32 (0.10–0.54) $P = .0038$
Current heroin use	−2.5 (−3.5 to −1.47) $P < .0001$	Nadir CD8, doubling	0.21 (−0.16 to 0.57) $P = .26$
BMI, kg/m^2	0.077 (0.024–0.13) $P = .0041$	Nadir WBC, doubling	1.56 (−0.58 to 3.7) $P = .15$
Waist circumference, /10 cm	0.17 (−0.067 to 0.41) $P = .16$	Nadir T lymph, doubling	0.66 (0.20–1.11) $P = .0047$
Parity	0.10 (−0.064 to 0.26) $P = .23$	HCV	−2.4 (−3.1 to −1.60) $P < .0001$
Ever pregnant	−0.22 (−1.47 to 1.03) $P = .73$	History of AIDS	−1.81 (−2.5 to −1.13) $P < .0001$
Age at menarche	0.12 (−0.063 to 0.30) $P = .20$	NRTI use	0.27 (−0.37 to 0.92) $P = .41$
History of weight loss	−0.87 (−1.57 to −0.18) $P = .014$	NNRTI use	1.10 (0.030–2.2) $P = .044$
Undetectable HIVRNA	1.28 (0.45–2.1) $P = .0026$	PI use	0.99 (0.17–1.81) $P = .017$
HIVRNA, /10-fold	−0.71 (−0.98 to −0.44) $P < .0001$	HAART use	1.18 (0.45–1.92) $P = .0016$

Estimates from NLMIXED model for mixture of normal distributions incorporating left, right, interval censoring for age at final menstrual period.

AMH, antimüllerian hormone; *BMI*, body mass index; *CI*, confidence interval; *HCV*, hepatitis C virus; *WBC*, white blood cell.

[a]AMH at age 40 y estimated using fitted random intercept from left-censored regression model–covariates selected from visit closest to age 40 y.

TABLE 3

Multivariable-adjusted associations of antimüllerian hormone at age 40 years[a] and other parameters with age at final menstrual period

Parameter	Multivariable adjusted Model 1 Estimate in years (95% CI)	Multivariable adjusted Model 2 Estimate in years (95% CI)
AMH at age 40 y, per doubling	1.49 (1.36–1.63) $P < .0001$	1.49 (1.36–1.62) $P < .0001$
Current smoker	−1.27 (−1.79 to −0.75) $P < .0001$	−1.18 (−1.69 to −0.66) $P < .0001$
CD4 count >500	0.54 (0.0093–1.06) $P = .046$	
HIVRNA, /10-fold		−0.27 (−0.47 to −0.071) $P = .0079$
HCV	−0.90 (−1.45 to −0.35) $P = .0014$	−0.81 (−1.37 to −0.26) $P = .0041$
History of AIDS	−0.84 (−1.35 to −0.34) $P = .0010$	−0.91 (−1.40 to −0.41) $P = .0003$
AICC [smaller is better]	6189.4	6186.1

Estimates from NLMIXED model for mixture of normal distributions incorporating left, right, interval censoring for age at final menstrual period.

AICC, corrected Akaike information criterion; *AMH*, antimüllerian hormone; *CI*, confidence interval; *HCV*, hepatitis C virus.

[a]AMH at age 40 y estimated using fitted random intercept from left-censored regression model.