HIV Infection, Drug Use, and Onset of Natural Menopause

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Objective. To study the relationship of HIV infection and drug use with the onset of natural menopause.

Methods. Our analyses used the World Health Organization's definition of menopause (i.e., the date of the last menstrual period is confirmed after 12 months of amenorrhea) and baseline data from a prospective study. Semiannual interviews were conducted. Levels of HIV antibody and $CD4^+$ cell counts were obtained. Menopause was identified at baseline or during 12 months of follow-up. Women ingesting reproductive hormones were excluded. Logistic regression analyses were used to assess factors associated with menopause.

Results. Of 571 women, 53% were HIV infected, and 52% had used heroin or cocaine in the previous 5 years. The median age was 43 years (interquartile range [IQR], 40–46 years); 48.9% of the women were black, 40.4% were Hispanic, and 10.7% were white. The median body mass index was 29.1 kg/m^2, and 90.4% of participants were current or former cigarette smokers. Menopause was identified in 102 women: 62 HIV-infected women (median age, 46 years; interquartile range [IQR], 39–49 years) and 40 uninfected women (median age, 47 years; IQR, 44.5–48 years).

Factors independently associated with menopause included HIV infection (adjusted odds ratio [OR], 1.73; 95% confidence interval [CI], 1.075–2.795), drug use (adjusted OR, 2.633; 95% CI, 1.610–4.308), and physical activity (adjusted OR, 0.895; 95% CI, 0.844–0.950). Among HIV-infected women, factors independently associated with menopause included $CD4^+$ cell counts of >500 cells/mm^3 (adjusted OR, 0.191; 95% CI, 0.076–0.4848) and 200–500 cells/mm^3 (adjusted OR, 0.356; 95% CI, 0.147–0.813).

Conclusion. Our study shows that HIV infection and immunosuppression are associated with an earlier age at the onset of menopause. Whether early onset of menopause in HIV-infected women increases their risk of osteoporosis and heart disease requires further study.

Among the 40 million women estimated to reach menopause during the next decade, HIV-infected women comprise a medically important but overlooked subgroup [1]. In the United States, women with HIV infection are living longer because of HAART [2]. Of women in the United States with HIV infection with or without AIDS, one-fourth have injected drugs, and many more have used drugs by other routes [3]. However, no published studies to date have examined how HIV infection, HAART, illicit drug use, and immune status affect the onset of menopause.

Menopause has been investigated mainly in middle-class, white women, among whom the median age at the onset of menopause has been reported to be 50–52 years [4, 5]. The onset of menopause has been associated with an increased risk for many medical illnesses [6], including cardiovascular disease, diabetes, and osteoporosis, and an earlier age at the onset of menopause increases the risk for these diseases [7–9]. Furthermore, early age at the onset of menopause has been linked to increased mortality [10–11]. For women with HIV infection, an earlier age at the onset of menopause could potentially add to the underlying risk for dyslipidemia, insulin resistance, and osteopenia conferred by HIV infection and receipt of HAART [12–15].

The most consistent epidemiologic predictor of earlier age at the onset of menopause is cigarette smoking,

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with menopause occurring 1–2 years earlier in smokers, compared with nonsmokers [5, 16–18]. Markers of low socioeconomic status have also been associated with earlier age at the onset of menopause, including a lower level of education and unemployment [7, 19–20]. In some studies, African American women have been observed to reach menopause earlier than have white women, which is thought to be partly caused by psychological stress [21]. Smoking is common among HIV-infected women and ubiquitous among drug users. HIV-infected women are largely poor and undereducated, with a socioeconomic status markedly below that observed in the populations studied in the general menopause literature [22]. Moreover, African American women have the highest rate of HIV infection with or without AIDS, compared with the rate among Hispanic and non-Hispanic white women in the United States [3]. These factors led us to hypothesize that HIV-infected women are at increased risk for an earlier onset of menopause than are uninfected women, independent of age. Therefore, we undertook this investigation into the relative effects of HIV infection, HAART, illicit drug use, and changes in $CD4^+$ cell counts on the occurrence of natural menopause.

METHODS

The "Ms Study" is a prospective study of the natural history of menopause among HIV-infected and drug-using women in the Bronx, New York, as previously described [23]. Between September 2001 and September 2003, women aged 35–59 years were recruited from primary care clinics and methadone programs and through community newsletters. The study was designed to consist of 50% HIV-infected women and 50% uninfected women, and within each of these groups, 50% were to be drug users. Semi-annual standardized interviews were conducted in either English or Spanish by trained research staff. Height and weight were measured to calculate body mass index values (kg/m^2), which were categorized according to Centers for Disease Control and Prevention criteria [24]. Blood samples were tested for HIV antibodies and, for HIV-infected women, were used to obtain $CD4^+$ cell counts. Participants were reimbursed for time spent in the research visit. The study was approved by the institutional review board of the participating hospital and medical school, and all participants provided written, informed consent.

The study interview elicited information regarding sociodemographic characteristics, medical and reproductive histories, physical activity, depression, cigarette smoking, drug use, and history of alcohol use. For HIV-infected women, information regarding use of antiretroviral medications was elicited. HAART was defined according to current guidelines [25].

Data regarding drug use and route of administration in the 5 years prior to baseline or prior to menopause (at which point these data are censored) were examined for use of heroin, cocaine, crack, and "speedball" (heroin-cocaine admixtures). The first and last years of use of each drug or combination of drugs was available for analysis. Physical activity was assessed by means of a composite of self-reported data regarding the intensity of daily housework, walking outdoors, and stair-climbing (a routine aspect of using the subway in New York City). We assessed histories of diabetes, hypertension, and heart disease using only diagnoses that preceded the year in which the last menstrual period occurred.

Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale [26]. Scores were stratified into the following categories: <16, 16–22, and $\geqslant 23$. Although a score of 16 has been used to suggest depressive symptomatology, a score of 23 has been used as a cutoff point in studies of similar populations that generally report higher scores [27–28].

Outcome variable. The outcome variable for this study is onset of natural menopause, which we defined, on the basis of the World Health Organization's (WHO's) criteria [29], as at least 12 consecutive months of amenorrhea not caused by surgery or another obvious cause, such as extreme weight loss. Age at onset of menopause was determined as of the date of the last menstrual period, after WHO criteria were met. Women who reported amenorrhea for $\geqslant 12$ months at their first visit were included. Entry into the menopausal transition (perimenopause) was defined as absence of menses in at least 3 cycles but for <12 months in the past year. A perimenopausal classification was retained until evidence of completion of menopause was obtained. For women who experienced onset of menopause at or just before the baseline interview, there was an average of 1 year of follow-up interviews for confirmation of menopause. Women receiving hormone replacement therapy or who had a history of undergoing hysterectomy and/or bilateral oophorectomy were excluded from this analysis.

Statistical methods. Initial analyses of menopause status and age at the last menstrual period were performed with χ^2, Wilcoxon rank sum, or Kruskal-Wallis tests. Logistic regression models identified factors associated with the binary outcome variable, natural menopause. For analyses of onset of menopause, age at baseline or at onset of menopause centered on the cohort's median age at onset of menopause was included in logistic regression models to study factors that increase or decrease the likelihood of menopause apart from age. Separate models were constructed for the HIV-infected women to examine the interrelationship of $CD4^+$ cell count, treatments for HIV infection, and other risk factors. All statistical analyses were performed with Stata software, version 8.0 (Stata).

RESULTS

Participant characteristics. There were 620 women enrolled in the study. Twenty-two women who had undergone surgical

menopause, 24 women receiving hormone replacement, and 3 women with missing and/or unreliable interview data were excluded. The analysis included 571 women. The median age was 43 years (interquartile range [IQR], 40–46 years).

As shown in table 1, 52.9% of the women were HIV infected, with a median $CD4^+$ cell count of 453 cells/mm^3. The study population was primarily African American (48.9%) and Hispanic (40.4%), with 8.6% of it being white and 2.1% being other races. The level of education attained was low: 44.3% had not completed high school. Only 21.7% of the women were currently employed ⩾20 h per week. Of the study population, 59% reported that they did not live with or have a current sex partner (man or women, married or common-law).

The median age at menarche was 12 years (range, 8–19 years). Most women (71.5%) were multiparous, with a median of 2 live births and a maximum of 13; 11.6% of the women reported having no live births. The median age at the time of the first pregnancy was 17 years (range, 11–38 years). The median age at the time of the last pregnancy was 31 years (range, 13–48 years). For HIV-infected women, the median body mass index was 27.3 (range, 14.7–54.0), and for uninfected women, the median body mass index was 32.1 (range, 18.9– 54.9).

Fifty-two percent (299 of 571) of women had a history of illicit drug use in the 5 years prior to baseline or onset of menopause. Of these drug users, 44.8% had a history of injection drug use, with no difference according to HIV status, and 96% had used multiple substances either simultaneously or sequentially. In the 5 years prior to baseline or onset of menopause, 88.3% of women had a history of using cocaine in some form, and 42.5% had a history of using cocaine and opiates. Compared with HIV-seronegative women, HIV-infected women were more likely to be using drugs during the 5-year baseline period (56.9% vs. 48.3%; $P = .04$). Only 9.6% of the study population reported never smoking cigarettes; although 22.6% had stopped smoking, 66.8% were current smokers who started smoking at a median age of 14 years. Twenty-five percent of women reported having been treated for alcohol abuse, and 8% reported current, daily consumption of alcohol. Alcohol use (frequency and history of treatment) did not differ by HIV status.

Age at natural menopause. Of 571 women, 102 (17.8%) met the criteria for menopause at a median age of 47 years (IQR, 42–48 years). Median age at onset of menopause was 46 years (IQR, 39–49 years) for HIV-infected women, compared with 47 years (IQR, 44.5–48 years) for HIV uninfected women. Among menopausal women, 26% of HIV-infected women, compared with 10% of uninfected women, experienced onset of menopause at <40 years of age ($P = .04$). An earlier age at onset of menopause was reported among women with less than a high school level of education, compared with women who had attained a high school degree (43.5 years [IQR, 38–47] vs. 47 years [IQR, 39–48 years]). Women reporting drug use in the 5 years prior to onset of menopause had median ages at onset of menopause of 43 years (IQR, 38–47 years) among heroin users and 46 years (IQR, 39–48 years) among cocaine users, compared with 47 years (IQR, 45–50 years) among women with no history of heroin or cocaine use in the 5 years prior to onset of menopause. Women reporting the least physical activity had an earlier median age at onset of menopause of 45 years (IQR, 41–48 years), compared with 47 years (IQR, 43–49 years) among the most physically active women. Median age at onset of menopause was not different in relation to race and/or ethnicity, cigarette smoking status, body mass index value, or frequency of alcohol use.

Factors associated with menopause. Table 1 displays characteristics of our cohort and factors associated with the onset of menopause. Significance testing reflects age-adjusted comparison of women in the menopause group with other women in the cohort who have not experienced onset of menopause. HIV infection was significantly associated with onset of menopause ($P = .03$). The frequency of illicit drug use (i.e., use of heroin and/or cocaine) in the 5 years prior to onset of menopause or baseline of the study was associated with onset of menopause ($P < .01$). Both cocaine use and heroin use were associated with onset of menopause ($P = .01$ and $P < .01$, respectively), with overlap in the use of these drugs. For HIV-infected women, the proportion of women experiencing onset of menopause increased as the $CD4^+$ count decreased ($P = .01$). Of the additional variables examined, only parity and physical activity were significantly associated with onset of menopause. Receipt of HAART (with or without protease inhibitors) was not associated with onset of menopause.

Multivariate analysis results. Factors independently associated with menopause were investigated by logistic regression, with adjustment for age at study entry (table 2). Women with HIV infection were 73% more likely to experience onset of menopause, compared with HIV uninfected women (adjusted OR, 1.734; 95% CI, 1.075–2.795), and women using cocaine and/or opiates were 2.60 times more likely to experience onset of menopause, compared with non–drug-using women (adjusted OR, 2.633; 95% CI, 1.610–4.308). Physical activity was inversely related to onset of menopause (adjusted OR, 0.895; 95% CI, 0.844–0.950). Being nulliparous and having 1 live birth were associated with onset of menopause (adjusted OR, 3.317; 95% CI, 1.643–5.992), compared with having ⩾4 live births. Race and/or ethnicity, level of education, employment status, age at the time of menarche, body mass index, alcohol use, cigarette smoking status, having experienced stressful life events, and having depressive symptomatology were not associated with onset of menopause.

In a logistic regression model of risk of menopause limited to HIV-infected women, the level of immunosuppression increased the likelihood of onset of menopause (table 3). After

Table 1. Characteristics of all women enrolled in the Ms Study and women meeting the World Health Organization's definition of menopause and the median age at which they experienced onset of menopause.

Variable	Proportion (%) of subjects		Age at onset of menopause, median years[a]	P[b]
	Women in the Ms Study (N = 571)	Women with menopause (n = 102)		
HIV status				
Infected	302/571 (52.9)	62/302 (20.5)	46	.030
Not infected	269/571 (47.1)	40/269 (14.9)	47	
Employment status				
Employed	124/571 (21.7)	19/124 (15.3)	47	.473
Unemployed	447/571 (78.3)	83/447 (18.6)	46	
No. of years of education				
⩾12 years	318/571 (55.7)	56/318 (17.6)	47	.364
<12 years	253/571 (44.3)	46/253 (18.2)	43.5	
Has sex partner				
Yes	233/571 (40.8)	31/233 (13.3)	47	.075
No	338/571 (59.2)	71/338 (21.0)	46	
Race				
African American	279/571 (48.9)	42/279 (15.1)	47	.150
Hispanic	231/571 (40.4)	44/231 (19.0)	46	.711
White or other	61/571 (10.7)	16/61 (26.2)	47	Ref
No. of live births				
0–1 birth	163/571 (28.6)	41/163 (25.1)	46	.001
2–3 births	244/571 (42.7)	42/244 (17.2)	47	.069
⩾4 births	164/571 (28.7)	19/164 (11.6)	47	Ref
CES-D scale score				
<16	242/571 (42.4)	39/242 (16.1)	46.5	.419
16–22	107/571 (18.7)	19/107 (17.8)	46	
⩾23	222/571 (38.9)	44/222 (19.8)	47	
Diabetes				
Yes	65/571 (11.4)	16/65 (24.6)	46	.367
No	506/571 (88.6)	86/506 (17.0)	47	
Hypertension				
Yes	176/571 (30.8)	38/176 (21.6)	47	.350
No	395/571 (69.2)	64/395 (16.2)	46	
Heart disease				
Yes	44/571 (7.7)	9/44 (20.4)	46	.905
No	527/571 (92.3)	93/527 (17.6)	47	
BMI				
<18.5	8/571 (1.4)	2/8 (25.0)	41	.148
18.5–24.9	141/571 (24.7)	34/141 (24.1)	46	
25–29.9	167/571 (29.2)	28/167 (16.8)	47	
⩾30	255/571 (44.7)	38/255 (14.9)	46.5	
Intensity of physical activity				
Very low[c]	131/571 (22.9)	34/131 (26.0)	45	<.0001
Low	137/571 (24.0)	28/137 (20.4)	45	
Moderate	157/571 (27.5)	24/157 (15.3)	47	
Active	146/571 (25.6)	16/146 (15.4)	47	
Cigarette smoking status				
Never smoked	55/571 (9.6)	7/55 (12.7)	47	.334
Formerly smoked	127/571 (22.2)	26/127 (20.5)	46	
Smokes <10 cigarettes per day	149/571 (26.1)	25/149 (16.8)	46	
Smokes 10–19 cigarettes per day	128/571 (22.4)	25/128 (19.5)	47	
Smokes ⩾20 cigarettes per day	112/571 (19.6)	19/112 (17.0)	47	

(*continued*)

Table 1. ***(Continued.)***

Variable	Proportion (%) of subjects		Age at onset of menopause, median years[a]	P[b]
	Women in the Ms Study (N = 571)	Women with menopause (n = 102)		
Alcohol use				
Daily	46/571 (8.0)	11/46 (23.9)	47	.873
Less than once per day	215/571 (37.7)	35/215 (16.3)	48	
None	310/571 (54.3)	56/310 (18.1)	45	
Received treatment for alcohol abuse				
Yes	143/571 (25.0)	23/143 (16.1)	46	.525
No	427/571 (75.0)	79/427 (18.5)	47	
Use of heroin and/or cocaine in the past 5 years				
Yes	299/571 (52.4)	68/299 (22.7)	45.5	<.001
No	272/571 (47.6)	34/272 (12.5)	47	
Use of heroin in the past 5 years				
Yes	162/571 (28.4)	44/162 (27.2)	43	.001
No	409/571 (71.6)	58/409 (14.2)	47	
Use of cocaine in the past 5 years				
Yes	264/571 (46.2)	58/264 (22.0)	46	.012
No	307/571 (53.8)	44/307 (14.3)	47	
HIV infection, by $CD4^+$ cell count				
<200 cells/mm^3	42/302 (13.9)	16/42 (38.1)	42.5	.009
200–500 cells/mm^3	134/302 (44.4)	28/134 (20.9)	46	
>500 cells/mm^3	126/302 (41.7)	18/126 (14.3)	46.5	
HIV infection, by HAART regimen				
With PI	113/302 (37.4)	28/113 (24.8)	45	.877
Without PI	82/302 (27.2)	14/82 (17.1)	48	.223
None	107/302 (35.4)	27/107 (25.2)	43	Ref

NOTE. BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression; PI, protease inhibitor; Ref, reference.

[a] Median age at menopause was 47 years for the 102 women meeting the WHO definition.

[b] P values are based on age-adjusted log-odds of menopause for each single variable.

[c] Physical activity is an ordinal measure from no strenuous housework, rarely walking outdoors, and rarely climbing stairs to frequent strenuous housework, walking >30 min per day, and daily climbing of stairs.

controlling for drug use, parity, physical activity, and age, a $CD4^+$ cell count of >500 cells/mm^3 (adjusted OR, 0.191; 95% CI, 0.076- 0.484) and a $CD4^+$ cell count of 200–500 cells/mm^3 (adjusted OR, 0.346; 95% CI, 0.147- 0.813) were independently associated with a decreased risk of onset of menopause, when compared with women who had a $CD4^+$ cell count of <200 cells/mm^3. Receipt of HAART was not significantly associated with onset of menopause.

DISCUSSION

HIV-infected women are now living long enough to experience menopause; to date, however, these women have been overlooked in most studies of menopause. Our study shows that HIV infection, its attendant lower immune function, use of cocaine and/or opioids, and physical inactivity were independently associated with age-adjusted onset of menopause. Moreover, the age at onset of menopause for HIV-infected and HIV-uninfected women was considerably lower than the age reported in the general menopause literature.

McKinlay et al. [4] reviewed the menopause literature from 1960 to 1982 and found that the median ages of white women at onset of menopause were remarkably consistent across studies, falling between 50 and 52 years. The Massachusetts Health Study [5] followed 2014 white women and observed a median age of 50.7 years. In an ongoing prospective study of multiethnic women, the Study of Women Across the Nation reported a median age of 51.5 years, after adjustment for multiple factors [7]. In sharp contrast, for women in the Ms Study, the unadjusted median age was 46 years for HIV-infected women and 47 years for HIV-uninfected women. Cejtin et al. [30] reported a median age at onset menopause of 47.7 years for HIV-infected women and 48.0 years for HIV-uninfected women enrolled in the Women's Interagency HIV Study. This analysis was also cross-sectional and defined onset of menopause as having occurred after 6 months of amenorrhea and achievement a follicle-stimulating hormone level of >25 mIU/mL. These results are similar to our findings regarding an earlier onset of menopause in women with and at risk for HIV infection, especially

Table 2. Factors associated with menopause, by logistic regression analysis of all women enrolled in the Ms Study ($n = 571$).

Factor	Adjusted OR (95% CI)	*P*
HIV-infected vs. noninfected	1.734 (1.075–2.795)	.024
Drug use vs. no drug use	2.633 (1.610–4.308)	<.0001
Physical activity[a]	0.895 (0.844–0.950)	<.0001
No. of live births		
0–1 birth	3.317 (1.643–5.992)	.001
2–3 births	1.901 (1.017–3,557)	.044
⩾4 births	Ref	…
Age at baseline in years[b]	1.179 (1.116–1.245)	<.0001

NOTE. Ref, reference.

[a] Ordinal variable from 3 to 18.

[b] Continuous variable centered on median age at onset of menopause.

compared with results of other studies [4]. However, identifying onset of menopause by observation of a brief duration of amenorrhea and measurement of follicle-stimulating hormone levels differs substantially from the definition of menopause used in our study. We used a definition consistent with the definition recommended by the WHO and a recent consensus panel [31] and the definition used in the Study of Women Across the Nation.

Among HIV-infected women, a higher $CD4^+$ cell count was associated with a decreasing likelihood of onset of menopause. The women with $CD4^+$ cell counts of <200 cells/mm^3 had the earliest onset of menopause, with a median age at onset of 42.5 years. Although women with more advanced HIV infection and potentially lower body weight and/or wasting may be more likely to be amenorrheic, evidence that body mass index or weight and onset of menopause are associated is inconsistent [17, 21] or absent [7]. Furthermore, our study showed no association between body mass index and onset of menopause. Few women had a body mass index low enough to be a likely cause of amenorrhea (i.e., <18.5). Harlow et al. [32] analyzed menstrual calendar data obtained from 2 large cohorts of HIV-infected women aged 20–44 years and found associations between increased cycle variability and episodes of amenorrhea and a $CD4^+$ cell count of <200 cells/mm^3. In that study, it is possible that the women with a low $CD4^+$ cell count and abnormal menstrual findings were already experiencing menopause transition, particularly given that earlier onset of menopause is associated with immunosuppression and HIV infection in our study.

We assessed histories of drug use in the 5-year period prior to onset of menopause or baseline (for women who had not reached menopause), instead of current drug use, because the 5-year period would more closely overlap the menopause transition, a process that takes many years to complete [31]. We combined use of cocaine and heroin to reflect the high frequency of multiple drug use in our population [33–34]. Although heroin and cocaine use were each associated with onset of menopause, the strongest association in multivariate models was with any use of heroin, cocaine, and their admixtures. Several studies of largely premenopausal women have shown that heroin use and cocaine use are each associated with cycle periods of amenorrhea in excess of 3 months and anovulation [35–37]. These studies suggest that, in younger premenopausal women, opioid use may be associated with hypogonadotropic hypogonadism. Unfortunately, data regarding older or perimenopausal women are lacking. The likelihood that 12 months of amenorrhea is a result of menopause and not hypogonadotropic hypogonadism is likely to be higher in older drug-using women. Use of cocaine and opioids has been related to decreased central neural drive to the reproductive system, which is attributed to drug-induced hyperprolactinemia. This mechanism limits the usefulness of measuring follicle-stimulating hormone levels in classifying the menopausal status of drug-using women [38–40]. Our strong finding of the association between drug use and onset of menopause requires additional confirmation, ideally with a correlation of markers of ovarian function, such as the mullerian-inhibiting factor, which is independent of the hypothalamic-pituitary axis [41].

We did not find an association between receipt of HAART and onset of menopause. HAART was initiated relatively recently for women enrolled in the Ms Study, compared with the decades of illicit drug use that largely began during premenopause and spanned the menopausal transition, with intermittent periods of intense use. Similarly, $CD4^+$ cell count was related to age at onset of menopause, and although there was no statistical interaction with receipt of HAART, the known increase in the level of $CD4^+$ cell count associated with HAART may have led to a higher age at onset of menopause among

Table 3. Factors associated with onset of menopause by logistic regression limited to HIV-infected women ($n = 302$).

Factor	Adjusted OR (95% CI)	*P*
$CD4^+$ cell count		
>500 cells/mm^3	0.191 (0.076–0.484)	<.0001
200–500 cells/mm^3	0.346 (0.147–0.813)	.015
<200 cells/mm^3	Ref	…
Drug use vs. no drug use	2.534 (1.321–4.861)	.005
Physical activity[a]	0.756 (0.790–0.928)	<.0001
No. of live births		
0–1 birth	4.580 (1.753–11.965)	.002
2–3 births	2.913 (1.166–7.278)	.022
⩾4 births	Ref	
Age at baseline in years[b]	1.146 (1.072–1.225)	<.0001

NOTE. Ref, reference.

[a] Ordinal variable from 3 to 18.

[b] Continuous variable centered on median age at onset of menopause.

HAART recipients, compared with that of non-HAART recipients. The effect of HAART may have become undetectable, relative to the stronger effects of drug use and $CD4^+$ cell count.

Although changes in reproductive hormones and anovulation have been linked to strenuous exercise in young athletes, there is a paucity of data regarding exercise and onset of menopause, particularly among persons with high body mass indices [42–43]. Bromberger et al. [21] found no effect of exercise on age at onset of menopause among healthy US women. The level of physical activity typical of women in our study (based on intensity of housework, climbing stairs in buildings and subways, and walking outdoors) was significantly related to onset of menopause, with the more active women having a later onset. In our population, the level of physical activity may be a marker of health status independent of HIV infection and $CD4^+$ cell count, which is related to a later onset of menopause.

We did not find that cigarette smoking affected onset of menopause, in contrast to the published literature [17–18], as 90.4% of participants in our study were current or former smokers. The high prevalence of smoking among drug users limits the study of the relative importance of cigarette smoking and drug use to onset of menopause.

Neither race/ethnicity nor socioeconomic indicators were associated with onset of menopause in our study. African American race has been inconsistently associated with an earlier onset of menopause [7]. Our study predominantly consisted of African American and Hispanic women of Puerto Rican descent who were, for the most part, poor and undereducated. This may have limited our ability to discern whether socioeconomic status or race and/or ethnicity was associated with onset of menopause. However, these factors may have contributed to the earlier age at onset of menopause in the entire cohort, compared with estimates for middle-class, predominantly white women.

A limitation of the study includes the possibility that, for some women, amenorrhea lasting for $\geqslant$12 months was related to drug use or other factors and not onset of menopause. In addition, our analysis was the baseline period of a longitudinal study and was, therefore, cross-sectional. As our study accrues incident cases of menopause, estimates of age at onset of menopause can be defined more precisely.

This study demonstrates effects of HIV infection, $CD4^+$ cell count, drug use, and physical activity on the risk of onset of natural menopause and suggests that HIV-infected and at-risk uninfected women can expect to experience menopause at 46–47 years old, which is markedly younger than the age estimate of 50–52 years for middle-class, predominantly white American women. A better understanding of the menopause transition for HIV-infected women will help to optimize their care as they age.

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