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Factors Associated with Preclinical Disability and Frailty among HIV-Infected and HIV-Uninfected Women in the Era of cART

Arpi S. Terzian, Ph.D., M.P.H.,[1] Susan Holman, R.N., M.S.,[2] Niyati Nathwani, M.D.,[3] Esther Robison, Ph.D.,[4] Kathleen Weber, B.S.N.,[5] Mary Young, M.D.,[6] Ruth M. Greenblatt,[7] and Stephen J. Gange, Ph.D.,[1] for the Women's Interagency HIV Study

Abstract

Background: HIV-associated immune injury is hypothesized to increase the risk of preclinical disability and frailty via inflammatory pathways. We investigated the role of $CD4^+$ T cell depletion and clinical AIDS on preclinical disability and frailty in HIV-positive women with a history of combination antiretroviral therapy (cART) and HIV-negative women.

Methods: This was a cross-sectional study nested within the Women's Interagency HIV Study (WIHS), a prospective cohort study initiated in 1994 across five U.S. cities. Questionnaires and tests were performed by 573 HIV-negative and 1206 HIV-positive women. Prevalence ratios were computed using regression models.

Results: Severe $CD4^+$ cell depletion was an independent predictor of slowness, weakness, and frailty in HIV-positive women compared with HIV-negative women. Women with $CD4^+$ counts <100 cells/mm^3 were 0.13 seconds slower to complete 4 meters (95% CI 0.06-0.21), 1.25 kg weaker (95% CI -2.31--0.19), and had 2.7 times higher prevalence of frailty (95% CI 1.46-5.01).

Conclusions: This study is one of the largest studies to administer performance-based tests to investigate disability and frailty in HIV-positive women. HIV-positive women with intact immune systems and without a history of clinical AIDS were no different from HIV-negative women on tests of slowness, weakness, and frailty phenotype.

Introduction

Combination antiretroviral regimens (CART) have led to sustained survival among individuals infected with human immunodeficiency virus (HIV). Some estimates show that among adults with AIDS in the era of cART, half will survive more than 16 years after AIDS diagnosis, in contrast to the estimated 1.2 years for AIDS patients from the no or single drug treatment era.[1] Individuals who begin therapy before progression to clinical AIDS may survive for even longer periods of time. Given this increased survival time, there is growing interest in evaluating how HIV infection and its treatment may impact broader measures of health in an aging population.[2–4]

Both HIV and aging are thought to impair cognitive, metabolic, and cardiovascular functioning.[2,5] Research is accumulating to suggest that deterioration of these physiological systems is caused in part by systemic immune activation and a chronic inflammatory state, which may persist even when HIV replication is adequately suppressed. In both HIV infection and aging, systemic immune activation causes impaired regenerative capacity and functioning of T cell populations that may hinder antigen-specific responses but may promote generalized inflammation.[6–10] Overproduction of

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.
[2]SUNY Downstate Medical Center, Brooklyn, New York.
[3]University of Southern California, Los Angeles, California.
[4]Montefiore Medical Center, Bronx, New York.
[5]The CORE Center at John H. Stroger Jr. Hospital of Cook County, Chicago, Illinois.
[6]Georgetown University Medical Center, Washington, D.C.
[7]University of California, San Francisco, California.

such proinflammatory cytokines as interleukin-6 (IL-6) has been associated with significant physiological effects, such as protein catabolism, bone mineral loss, reduced muscle mass, atherosclerosis, cognitive deficits, and heightened vulnerability to stress.[9,11,12] Chronic immune activation and inflammation have been implicated in the initiation of disability and frailty.[13–15] Preclinical disability and frailty are correlated with, but independent of, comorbidities, functional impairment, and age.[14–22] An analysis in the Multicenter AIDS Cohort Study (MACS) of a self-reported frailty-like phenotype found that HIV-positive men were associated with an earlier occurrence of a frailty-like phenotype compared with HIV-negative men.[7] We hypothesized that women with profound immunological injury, as measured by $CD4^+$ T cell depletion and history of clinical AIDS, would be at greater risk for preclinical disability and frailty than HIV-uninfected women. We assessed physical functioning end points in an ongoing prospective cohort study of HIV-positive and HIV-negative women: the Women's Interagency HIV Study (WIHS). By nesting this work in an existing cohort study, we capitalized on the availability of extensive clinical, behavioral, and psychosocial data.

Materials and Methods

Study population

The WIHS is a prospective cohort study designed to investigate the natural and treated history of HIV in women. Women were recruited at six sites across five U.S. cities: Bronx and Brooklyn, NY, Washington, DC, the San Francisco, CA, Bay Area, Los Angeles, CA, and Chicago, IL. A total of 3766 women were recruited to enroll in 1994–1995 and again in 2000–2001. To be eligible for participation, women had to be at least 13 years old, provide informed consent, have blood drawn for HIV testing, and travel to a clinical research site.[23] Informed consent was obtained in compliance with guidelines for human subject research as mandated by the U.S. Department of Health and Human Services and participating institutions.[24] WIHS study participants were scheduled to return every 6 months for follow-up. Visits included a structured interview, a physical examination, and specimen collection. Additional details on WIHS recruitment and characteristics have been described elsewhere.[23–26]

Definition of frailty

We assessed the prevalence of frailty using the syndromic-based definition proposed by Fried et al. that has been validated in several population-based studies, including the Cardiovascular Health Study (CHS).[13,21] The frailty phenotype is hypothesized to have its own pathophysiology and etiology that is not fully explained by disease, disability, or advanced age. Frailty consists of five characteristics: impaired mobility (slowness), reduced upper body strength (weakness), self-reported physical exhaustion, unintentional weight loss (sarcopenia), and low physical activity (energy expenditure). Specific measures included (1) a short questionnaire evaluating the ability to perform certain tasks, (2) a physical activity questionnaire (PAQ) capturing intensity and duration of 18 activities that range from work to child care, and (3) two performance-based tests: the timed-gait and grip-strength tests.

The physical functioning measures were adapted from the National Health and Nutrition Examinations Survey (NHANES) and the Established Population for the Epidemiologic Studies of the Elderly (EPESE). The timed-gait test, a measure of lower body functioning and mobility, was conducted using a walking course of 4 meters.[27] Participants were asked to walk the course at their usual pace and take the test twice. The grip-strength test, a measure of upper body strength, required participants to squeeze a hand-held Jamar dynamometer with maximum force using their dominant hand.[28] Women were asked to repeat this test three times. The PAQ was based on a modified version of the Minnesota Leisure Time Activities Questionnaire.[29] Impairments in mobility, strength, or physical activity, detected by these measures, have predicted preclinical disability and mortality in older disabled women.[30] Exhaustion was based on responses to two items from the CES-D scale.[31] Unintentional weight loss was assessed by self-reported weight loss of at least 10 lbs in the past year and confirmed by physical examination. Using data from self-reported questionnaires and performance-based tests at a single study visit, we estimated the prevalence of a frailty phenotype. We summed the number of five components of frailty, consistent with the CHS definition of frailty. Each component was treated as a dichotomous variable (impaired/not impaired), and women with at least three impaired components were considered frail; those with less than three were nonfrail.

Study sample

In 2005, women were asked to participate in a single-visit substudy on physical function. Among participants attending a 2005 semiannual visit, women who agreed to participate in the substudy and completed at least one of the tests or questionnaires were eligible for inclusion. Among HIV-positive women, women who were treatment naïve (<10% of substudy participants) were excluded because they represent a small atypical subset of women with very slow HIV progression. Women reporting missing limbs, prostheses, paralysis, or assistive devices were excluded from analyses on walking time or weakness. In models of frailty, these women were assigned missing values for the performance-based components. Because frailty analyses were limited to women with data on at least three of the five components of the frailty index, these women may or may not have been included in models of frailty.

Dependent variables

Slowness was modeled in two ways. Modeled as a separate outcome, slowness was treated as a continuous variable, a height-adjusted value based on the average walking times of two timed trials (seconds/meter, sec/m). Modeled as a component of frailty, slowness was transformed to a binary variable. Walking times were ranked, binned into quintiles, and then dichotomized. The bottom quintile represented slow or impaired women. Similarly, weakness, modeled as a separate outcome, was treated as a continuous variable, a body mass index (BMI)-adjusted value based on the maximum grip strength score of three trials (kilograms, kg). Modeled as a component of frailty, weakness was treated as a binary variable. BMI-adjusted strength scores were ranked, binned into quintiles, and dichotomized. Women with scores in the bot-

tom quintile represented weak or impaired women. Low physical activity was treated the same; women with the lowest weighted kilocalories in the bottom quintile represented low physical activity. Weighted scores of kilocalories expended per week were calculated, applying metabolic equivalents (MET) weights and following a standardized algorithm.[21,32]

We applied more stringent cutoffs for slowness, weakness, and low physical activity than that used in CHS because our participants were significantly younger than the female CHS participants (≥65 years). Cutoffs were based on the lowest 20% observed in our sample rather than the lowest 20% observed in CHS.

Independent variables

Biological specimens collected at study visits were used for immediate laboratory testing of HIV viral load and T cell lymphocytes for percent and total $CD4^+$ and $CD8^+$ T cell counts. CD4 T cell counts were measured using standard flow cytometric techniques at local laboratories certified by the NIH/NIAID Flow Cytometry Quality Assurance Program.[24] Plasma HIV viral load was quantified using nucleic acid sequence-based amplification commercial assays with a lower limit of quantification of 80 copies/mL (BioMerieux, Boxtel, NC). To be considered as having a history of cART in these analyses, participants self-reported using highly active antiretroviral therapy (HAART) either at the substudy visit or visit(s) prior to the substudy visit. HAART was defined using the Department of Health and Human Services guidelines.[26] Data on AIDS-defining illnesses were routinely collected and defined by the 1993 Centers for Disease Control and Prevention (CDC) class C clinical definition of AIDS.[33]

Exposure variables included the following markers of immune injury: concurrent $CD4^+$, concurrent ratio of $CD4^+/CD8^+$ counts, area under the curve (AUC) values for repeated $CD4^+$ measurements, and history of clinical AIDS. $CD4^+$ counts were treated as a categorical variable, based on cutoffs commonly used in clinical care. Ratios were ranked and categorized into quintiles, based on the distribution observed in HIV-positive participants.[34] History of $CD4^+$ cell depletion was captured in a single measure, using AUC for all available $CD4^+$ counts since enrollment. AUC is commonly used in characterizing longitudinal measures to integrate patterns over time and to discriminate individuals with high and low average biomarker values.[35] Self-reported clinical AIDS was treated as a binary variable (ever/never).

Sociodemographic exposure variables of interest included age, race/ethnicity, education, depressive symptoms, alcohol consumption, income, BMI, marital status, and smoking history. Depressive symptoms were measured using the CES-D scale. Other covariates included study site, HIV risk type, and hepatitis C virus (HCV) status. HCV was determined by antibody (Ab) and RNA testing at baseline.

Statistical analysis

Sociodemographic characteristics were stratified by HIV and compared using chi-square tests of association. Linear regression models were constructed to estimate the average difference in walking time and grip strength between HIV-positive women with varying levels of immune injury and HIV-negative women. Similarly, log linear regression models were constructed to estimate prevalence ratios for frailty.[36] All univariate models were age adjusted. Models using AUC were further adjusted for $CD4^+$ counts measured at the visit that immediately preceded self-reported HAART initiation.

Two types of multivariate models were constructed to control for confounding and assess mediation. The primary motivation for the first multivariate model (e.g., partially adjusted model) was to account for potential confounding at baseline (entry into WIHS). This model included age, race/ethnicity, educational attainment, depressive symptoms, HIV risk category, HCV status, alcohol consumption, income, BMI, marital status, smoking history, and study site. The second model is an extension of the first, considered the fully adjusted model because it included factors collected at both baseline and substudy visits The fully adjusted model was generated to improve residual confounding and detect potential mediation by comparing regression coefficients from both models. Analyses were conducted using SAS version 9.0 (SAS Inc., Raleigh, NC).

Results

Participant characteristics

Of the 1880 women who were seen in 2005, a total of 1781 (95%) participated in the substudy. No differences were observed between participants and nonparticipants by sociodemographic characteristics (data not shown). Women who were included in our analysis were 1208 HIV-positive/HAART-positive women (68%) and 573 HIV-negative women (32%). Nine women reported missing limbs, paralysis, prostheses, or assistive devices. Table 1 presents participant characteristics by HIV status. All characteristics differed by HIV except for race/ethnicity ($p < 0.05$). The median age (interquartile range) for HIV-positive and HIV-negative women was 41 years (36–47) and 38 years (30–45), respectively. Over one quarter of participants reported being of Hispanic descent. Over one half were African American. Among HIV-infected women, 20% had active HCV infection. In contrast, the prevalence of active HCV infection among HIV-uninfected women was 12%. These percentages were similar to percentages observed for HIV-positive and HIV-negative women reporting a history of injection drug use (21% and 17%, respectively).

Longer walking times

The number of HIV-positive and HIV-negative women who participated in the timed-gait test was 1124 and 539, respectively. The median walking times to complete the 4-meter test for HIV-negative women, HIV-positive women with $CD4^+$ counts ≥500 and <100 counts were 4.24, 4.28, and 5.08 seconds, respectively. After controlling for confounding by sociodemographic characteristics at baseline, HIV-positive women with concurrent $CD4^+$ counts <100 cells/mm^3 or AUC $CD4^+$ <100 cells/mm^3 were 0.52 seconds (95% CI 0.24-1.24) and 0.21 seconds (95% CI 0.03-0.52) slower to complete the distance than HIV-negative women. Estimates did not differ between the partially and fully adjusted models, suggesting that mediation via concurrent covariates was negligible. HIV-positive women with a history of AIDS also took more time to complete the timed walk. In addition to the independent effects of $CD4^+$ counts and age, older women

Table 1. Sociodemographic and Clinical Characteristics by HIV Status at Substudy Visit ($N = 1781$)

	HIV-negative n *(%)* *573 (32%)*	*HIV+/HAART+*[a] n *(%)* *1208 (68%)*	p *value*
Depressive symptoms (CES-D)			
None (<16)	392 (69)	725 (61)	<0.01
Moderate (16–19)	48 (8)	96 (8)	
Severe (20+)	130 (23)	371 (31)	
Body mass index			
Under (<18.5)	11 (2)	33 (3)	<0.0001
Normal (18.5–24)	135 (25)	411 (35)	
Over (25–29)	152 (27)	347 (30)	
Obese (30+)	251 (46)	371 (32)	
Education			
No schooling	1 (<1)	10 (1)	<0.001
Grades 1–6	6 (1)	66 (6)	
Grades 7–11	186 (32)	389 (32)	
High school	182 (32)	356 (29)	
Some college	151 (27)	302 (26)	
College+	45 (8)	82 (7)	
Race/ethnicity			
White/non-Hispanic	53 (9)	157 (13)	0.07
Hispanic	158 (28)	355 (30)	
Black/non-Hispanic	341 (59)	655 (54)	
Other	21 (4)	40 (3)	
Income			
>$18,000	316 (59%)	739 (67)	<0.001
$18,001–$24,000	54 (10%)	98 (9)	
$24,001–$30,000	37 (7%)	86 (8)	
$30,001–$36,000	36 (7%)	61 (5)	
$36,001–$75,000	72 (14%)	80 (7)	
>$75000	18 (3%)	47 (4)	
Age			
<30	140 (24)	101 (8)	<0.0001
30–39	181 (32)	389 (32)	
40–49	180 (31)	493 (41)	
50+	72 (13)	224 (19)	
Median (IQR)	38 (30, 45)	41 (36, 47)	
Marital status			
Married/ partner	178 (33)	372 (33)	<0.0001
Widowed/divorced/separate	87 (16)	347 (31)	
Never married/other	269 (51)	397 (36)	
Smoking history			
Never	291 (52)	541 (44)	<0.01
Former	118 (21)	286 (24)	
Current	151 (27)	374 (32)	
HCV status			
Active	66 (12%)	228 (20)	<0.0001
Resolved/negative	490 (88%)	910 (80)	
HIV risk category			
Intravenous drug use	96 (17%)	256 (21)	<0.0001
Heterosexual	151 (26%)	524 (44)	
Transfusion	9 (2%)	28 (2)	
No identified risk (Ref)	315 (55%)	391 (33)	

[a]HAART, highly active antiretroviral therapy; CES-D, Center for Epidemiologic Studies Depression Scale; IQR, interquartile range.

had longer walking times than younger women 10 years their junior by 0.12 seconds.

Weakness

The number of HIV-negative and HIV-positive women participating in the strength test was 534 and 1105, respectively. Compared with HIV-negative women, HIV-positive women were almost 3 kg weaker. Table 2 presents median kilogram values for hand grip strength by HIV status. Both HIV-negative women, and HIV-positive women with $CD4^+$ counts $\geq$500 were, on average, 2 kg stronger than HIV-positive women with $CD4^+$ counts <100 or clinical AIDS (30 vs. 28 kg). In partially adjusted models, HIV-positive

Table 2. Associations of Markers of Immunosuppression with Grip Strength (kg) in HIV-negative and HIV-positive Women with History of HAART ($N = 1639$)

	n	*Median strength (kg)*	*Age-adjusted univariate β (95% CI)*[a]	*Multivariate model 1*[b] *β (95% CI)*	*Multivariate model 2*[c] *β (95% CI)*
HIV-negative (Ref)	534	30			
$CD4^+$					
<100	78	28	−3.29 (−5.17-−1.42)*	2.75 (−4.61-−0.89)*	−1.53 (−3.56-0.49)
100–199	102	28	−1.48 (−3.17-0.20)	−0.86 (−2.56-0.84)	−0.83 (−2.67-1.01)
200–349	246	28	−1.23 (−2.43-−0.03)*	−0.52 (−1.74-0.69)	−0.16 (−1.45-1.13)
350–499	237	28	−1.06 (−2.27-0.15)	−0.11 (−1.35-1.13)	0.16 (−1.15-1.46)
≥500	425	30	−0.26 (−1.27-0.75)	0.22 (−0.81-1.25)	0.53 (−0.55-1.61)
AUC $CD4^+$[d]					
<100	135	26	−3.01 (−4.50-−1.52)*	−2.03 (−4.63-0.56)	−2.47 (−5.19-0.25)
100–199	239	28	−1.89 (−3.10-−0.68)*	−0.81 (−3.39-1.76)	−2.18 (−4.91-0.54)
200–349	370	29	−1.18 (−2.23-−0.13)*	−0.36 (−2.87-2.15)	−1.70 (−4.32-0.91)
350–499	239	30	0.03 (−1.17-1.23)	0.67 (−1.93-3.28)	−0.32 (−3.04-2.40)
≥500	106	30	−0.43 (−2.07-1.20)	−0.10 (−2.97-2.77)	−1.46 (−4.45-1.53)
$CD4^+/CD8^+$[e]					
≤0.29	234	28	−2.02 (−3.23-−0.80)*	−1.36 (−2.59-−0.13)*	−0.57 (−1.88-0.74)
0.30–0.46	216	28	−0.91 (−2.16-0.35)	<−0.01 (−1.27-1.26)	0.30 (−1.04-1.64)
0.47–0.63	223	28	−1.68 (−2.91-−0.45)*	−0.92 (−2.17-0.32)	−0.66 (−1.95-0.64)
0.64–0.93	212	28	−0.54 (−1.80-0.71)	0.16 (−1.11-1.42)	0.39 (−0.93-1.71)
≥0.94	202	30	0.41 (−0.86-1.69)	0.79 (−0.50-2.07)	1.19 (−0.16-2.53)
AIDS					
Yes	454	28	−1.94 (−2.96-−0.91)*	−1.25 (−2.31-−0.19)*	−0.51 (−1.64-0.63)
No	651	30	−0.51 (−1.42-0.39)	0.10 (−0.84-1.04)	0.33 (−0.65-1.31)

[a]CI, confidence interval.
[b]Multivariate model 1 was adjusted for current age, study site, race/ethnicity, baseline educational attainment, baseline depression, baseline hepatitis C virus, baseline frequency of alcohol consumption, baseline income, baseline BMI, baseline marital status, baseline smoking history, and baseline HIV risk category.
[c]In addition to covariates listed in multivariate model 1, model 2 was also adjusted for current depression, current frequency of alcohol consumption, current income, current BMI, current marital status, and current smoking history.
[d]AUC $CD4^+$, area under curve. Multivariate models were further adjusted for last $CD4^+$ count prior to HAART initiation.
[e]Concurrent ratio of $CD4^+/CD8^+$ is based on distribution of HIV-infected women.
*p value significant at $\alpha < 0.05$.

women with $CD4^+$ counts <100, AUC $CD4^+$ counts <100, $CD4^+/CD8^+$ ratios ≤0.29, and history of clinical AIDS were −2.75 kg (95% CI −4.61-−0.79), −2.86 kg (95% CI −5.55-−0,17), −1.87 kg (95% CI −3.14-−0.61), and −1.52 (95% CI −2.60-−0.43) weaker than HIV-negative women. Although no one marker was associated with weakness in the fully adjusted model, a gradient was observed for HIV-positive women by $CD4^+$ and AUC $CD4^+$ counts, where women with the lowest $CD4^+$ counts were most weak and those with the highest $CD4^+$ counts were least weak compared with HIV-negative women.

With respect to sociodemographic characteristics, women who were younger, without depressive symptoms, and with the lowest income were independently associated with stronger grip strength (Table 3). Compared with women who were at least 50 years of age, women who were <30, 30–39, and 40–49 were 3.97 kg (95% CI 2.27-5.66), 2.40 kg (95% CI 0.97-3.82), and 2.05 kg (95% CI 0.76-3.34), respectively, stronger in models controlling for $CD4^+$ counts and other sociodemographic factors.

Differences in grip strength were also observed by racial categories. Hispanic women were independently associated with weakness. In fully adjusted models, Hispanic women were −2.22 kg (95% CI −3.84-−0.60) weaker than white women.. African Americans were slightly stronger than white women, although differences were not statistically significant ($p > 0.05$). A nonstatistically significant trend was observed with BMI and strength, where HIV-positive women with the lowest BMI were the weakest compared with HIV-negative women, and these differences decreased with increasing levels of BMI. Coinfection with HCV was not associated with weakness.

Frailty

The number of HIV-positive and HIV-negative women who had complete data for the frailty index was 1206 and 573, respectively. Table 4 presents the prevalence of frailty phenotype by degree of $CD4^+$ cell depletion. The prevalence of frailty in HIV-negative women was 8%, compared with 12% in HIV-positive women with clinical AIDS or 20% in HIV-positive women with $CD4^+$ <100 cells/mm^3. Compared with HIV-negative women in partially adjusted models, HIV-positive women with concurrent $CD4^+$ counts <100 and $CD4^+/CD8^+$ ratio < 0.29 had 2.71 (95% CI 1.38-5.35) and 1.76 (95% CI 1.01-3.04) higher prevalence of frailty, although this increased prevalence did not persist in the fully adjusted model. Interaction between concurrent $CD4^+$ counts and age was not observed among HIV-positive women.

Table 3. Associations of Sociodemographic Characteristics with Grip Strength (kg) in HIV-negative and HIV-positive Women with History of HAART ($N = 1639$)

	Age-adjusted univariate[a] *β (95% CI)*[d]	*Multivariate model 1*[b] *β (95% CI)*	*Multivariate model 2*[c] *β (95% CI)*
HIV-negative (Ref)			
Depressive symptoms (CES-D)			
Baseline			
None (<16)	2.05 (1.24-2.86)*	1.92 (1.09-2.75)*	1.17 (0.25-2.10)*
Moderate (16–19)	1.04 (−0.27-2.36)	0.86 (−0.45-2.18)	0.33 (−1.02-1.68)
Severe (20+) (Ref)			
Concurrent			
None (<16)	2.48 (1.63-3.33)*		1.49 (0.52-2.45)*
Moderate (16–19)	1.52 (0.01-3.02)*		0.93 (−0.62-2.48)
Severe (20+) (Ref)			
Body mass index			
Baseline	0.09 (0.04-0.15)*	0.09 (0.04-0.15)*	0.06 (−0.04-0.16)
Concurrent	0.09 (0.04-0.14)*		0.06 (−0.04-0.15)
Education (baseline)			
No schooling	−8.95 (−13.95-−3.95)*	−7.00 (−11.90-−2.09)*	−6.34 (−11.26-−1.43)*
Grades 1–6	−7.80 (−10.13-−5.47)*	−4.08 (−6.56-−1.60)*	−2.42 (−5.09-0.24)
Grades 7–11	−2.84 (−4.38-−1.31)*	−1.90 (−3.56-−0.26)*	−0.97 (−2.73-0.78)
High school	−1.47 (−3.01-0.08)	−1.12 (−2.74-0.49)	−0.40 (−2.11-1.31)
Some college	−1.15 (−2.27-0.43)	−1.15 (−2.75-0.46)	−0.50 (−2.19-1.19)
College+ (Ref)			
Race/ethnicity			
Hispanic	−4.09 (−5.38-−2.80)*	−2.37 (−3.84-−0.91)*	−2.26 (−3.81-−0.70)*
Black/non-Hispanic	0.95 (−0.24-2.14)	1.98 (0.64-3.31)*	1.95 (0.52-3.37)*
Other	0.27 (−2.02-2.57)	0.15 (−2.27-2.56)	0.11 (−2.46-2.68)
White/non-Hispanic			
Income			
Baseline			
≤$6,000 or less	−0.95 (−2.83-0.92)	−0.68 (−2.57-1.22)	0.53 (−1.52-2.59)
$6,001–$12,000	−1.56 (−3.41-0.30)	−1.26 (−3.14-0.62)	0.10 (−1.93-2.14)
$12,001–$18,000	−0.66 (−2.68-1.36)	−0.23 (−2.26-1.81)	0.91 (−1.27-3.08)
$18,001–$24,000	−0.41 (−2.59-1.77)	−0.40 (−2.58-1.78)	0.96 (−1.38-3.30)
$24,001–$30,000	1.02 (−1.35-3.38)	0.21 (−2.14-2.56)	1.29 (−1.25-3.83)
$30,001–$36,000	−0.27 (−2.71-2.17)	−1.50 (−3.94-0.93)	−1.40 (−3.99-1.19)
$36,001–$75,000	1.04 (−1.24-3.32)	0.26 (−2.02-2.54)	0.86 (−1.54-3.27)
>$75,000 (Ref)			
Concurrent			
<$18,000	−5.02 (−7.04-−3.01)*		−4.01 (−6.37-−1.65)*
$18,001–$24,000	−4.58 (−6.93-−2.23)*		−3.63 (−6.24-−1.02)*
$24,001–$30,000	−3.71 (−6.12-−1.29)*		−3.71 (−6.34-−1.08)*
$30,001–$36,000	−3.77 (−6.29-−1.26)*		−3.16 (−5.86-−0.45)*
$36,001–$75,000	−3.17 (−5.50-−0.84)*		−3.40 (−5.86-−0.94)*
>$75,000 (Ref)			
Age			
<30	4.44 (3.03-5.85)*	4.65 (3.06-6.24)*	4.05 (2.36-5.75)*
30–39	2.35 (1.18-3.52)*	2.79 (1.46-4.12)*	1.96 (0.54-3.38)*
40–49	1.63 (0.50-2.77)*	1.95 (0.75-3.15)*	1.63 (0.36-2.91)*
50+ (Ref)			
Marital status			
Baseline			
Married/ partner	−0.15 (−1.19-0.89)	−0.33 (−1.38-0.73)	0.04 (−1.11-1.19)
Widowed/divorced/separate	1.10 (0.22-1.98)*	0.30 (−0.60-1.19)	0.26 (−0.78-1.30)
Never married/other (Ref)			
Concurrent			
Married/partner	−0.25 (−1.14-0.65)		0.20 (−0.87-1.28)
Widowed/divorced/separate	−1.16 (−2.16-−0.16)*		−1.03 (−2.24-0.18)
Never married/other (Ref)			
Smoking history			
Baseline			
Former	0.48 (−0.39-1.35)	−0.08 (−0.87-1.04)	−1.86 (−3.92-0.20)
Current	1.13 (−0.07-2.33)	0.79 (−0.43-2.01)	−0.63 (−2.88-1.62)
Never (Ref)			

(*continued*)

Table 3. (Continued)

	Age-adjusted univariate[a] *β (95% CI)*[d]	*Multivariate model 1*[b] *β (95% CI)*	*Multivariate model 2*[c] *β (95% CI)*
Concurrent			
Former	1.27 (0.37-2.17)*		2.39 (0.28-4.49)*
Current	1.07 (<0.01-2.14)*		1.40 (−0.74-3.54)
Never (Ref)			
Drink group			
Baseline			
Light (<3 drinks/week)	−0.49 (−1.90-0.92)	−0.87 (−2.34-0.60)	−0.79 (−2.36-0.78)
Moderate (3-13 drinks/week)	0.41 (−1.06-1.88)	−0.23 (−1.74-1.29)	−0.61 (−2.22-0.99)
Heavy (≥14 drinks/week)	0.06 (−1.55-1.68)	−0.58 (−2.21-1.05)	−0.61 (−2.30-1.08)
Abstainer (0 drinks/week) (Ref)			
Concurrent			
Light	−0.13 (−2.25-1.98)		−0.10 (−2.33-2.14)
Moderate	0.88 (−1.26-3.02)		0.32 (−1.94-2.57)
Heavy	1.98 (−0.37-4.32)		0.79 (−1.63-3.21)
Abstainer (0 drinks/week) (Ref)			

[a]Each variable is modeled separately. All models are adjusted for current $CD4^+$ All models were age-adjusted except for age.
[b]Multivariate model 1 was adjusted for current age, study site, race/ethnicity, baseline educational attainment, baseline depression, baseline hepatitis C virus, baseline frequency of alcohol consumption, baseline income, baseline BMI, baseline marital status, baseline smoking history, and baseline HIV risk category.
[c]In addition to covariates listed in multivariate model 1, model 2 was also adjusted for current depression, current frequency of alcohol consumption, current income, current BMI, current marital status, and current smoking history.
[d]CI, confidence interval; CES-D, Center for Epidemiologic Studies Depression Scale.
*p values significant at $\alpha = 0.05$.

Discussion

Among HIV-positive women with a history of cART, those with the greatest $CD4^+$ cell depletion were at higher risk for preclinical disability and frailty compared with HIV-negative women. Alternatively, HIV-positive women with intact immune systems and without a history of clinical AIDS were no different from HIV-negative women on tests of slowness, weakness, and frailty phenotype.

This study, to our knowledge, is the first to administer self-reported and performance-based measures to a large cohort of HIV-positive women in the United States. Women with the lowest $CD4^+$ and AUC $CD4^+$ counts had a higher prevalence of longer walking times, and lack of differences in walking times between HIV-positive and HIV-negative women may be explained by limitations of the test, as it likely failed to discriminate between high-risk and low-risk women for mobility-related disability. Tests with an endurance or speed component, such as walking a longer distance at a faster speed or climbing stairs for a set time, may have been more appropriate for this relatively high functioning group.[37]

Only HIV-positive women with the lowest $CD4^+$ counts at the substudy visit were weaker than HIV-negative women. This result, along with the observation that the majority of HIV-positive women had comparable grip strength with HIV-negative women, is consistent with previous investigations on disability among and between HIV-positive and HIV-negative adults. A study of the Veterans Aging Cohort Study (VACS) also noted differences in self-reported physical disability among HIV-infected veterans, where differences were most striking between symptomatic and asymptomatic patients, although no differences were observed between HIV-infected and HIV-uninfected veterans.[3] Moreover, grip strength in our cohort was comparable to normative grip strength values observed in participants of Studies of Women Across the Nation (SWAN), a cohort study of urban U.S. women who are of similar age and demographics.[38,39]

Women with $CD4^+$ counts < 100 and ratios of $CD4^+/CD8^+ < 0.29$ had a higher probability of frailty than HIV-negative women, where those with $CD4^+$ counts <100 had almost three times the prevalence. A study in a cohort of HIV-positive and HIV-negative men investigating a frailty-like phenotype, a self -reported measure containing fewer components of Fried's definition of frailty, found that HIV-infected men were almost 11 times more likely to report a frailty-like phenotype.[7] Markers of disease progression, such as $CD4^+$ counts <350, viral load <50,000, clinical AIDS, and duration of infection, also were associated with increased risk. Our findings, in conjunction with MACS and VACS studies, suggest that HIV does increase the risk of disability and frailty but is limited to those who have severe immunodeficiency. Because our study was cross-sectional and our sample had few women >50 years, it will be important to assess whether these and other results regarding frailty and disability continue to hold as more women attain older ages.[3,7]

Our study has a number of notable strengths. Standardized questionnaires, validated in such studies as the EPESE, CHS, and Women's Health and Aging Study, were employed. Findings may be transportable to other HIV-positive women in the United States in part because of our high level of participation. We recognize, however, the limitations of a single cross-sectional assessment of physical functioning. Temporal relationship between immune injury and incident preclinical disability could not be established. Our single measurement precluded examining within-individual changes in functioning by duration of HIV and changes in physical functioning

Table 4. Analyses of Markers of Immunosuppression with Frailty Phenotype in HIV-positive and HIV-negative Women with History of HAART ($N = 1779$)

	n	*Frail (%)*	*Age-adjusted univariate PR (95% CI)*[a]	*Multivariate model 1*[b] *PR (95% CI)*	*Multivariate model 2*[c] *PR (95% CI)*
HIV-negative (Ref)	573	8			
$CD4^+$					
<100	82	20	2.43 (1.37-4.32)*	2.89 (1.55-5.39)*	2.02 (1.01-1.11)*
100–199	117	14	1.36 (0.72-2.59)	1.46 (0.70-3.02)	1.05 (0.46-2.38)
200–349	267	9	1.15 (0.70-1.88)	1.20 (0.68-2.13)	1.04 (0.57-1.89)
350–499	255	10	1.26 (0.77-2.04)	1.21 (0.67-2.17)	1.22 (0.65-2.27)
≥500	466	6	0.77 (0.48-1.24)	0.84 (0.56-1.61)	0.93 (0.53-1.66)
AUC $CD4^{+d}$					
<100	151	17	2.02 (1.23-3.34)*	2.66 (0.98-7.22)	2.18 (0.75-6.32)
100–199	260	10	1.27 (0.78-2.08)	1.37 (0.47-3.99)	1.63 (0.54-4.93)
200–349	379	9	1.16 (0.74-1.80)	1.73 (0.62-4.80)	1.96 (0.66-5.85)
350–499	264	6	0.74 (0.41-1.34)	1.03 (0.33-3.22)	1.19 (0.36-3.95)
≥500	117	6	0.91 (0.41-2.03)	1.79 (0.49-5.98)	2.37 (0.64-8.81)
$CD4^+/CD8^{+e}$					
≤0.29	255	14	1.62 (1.03-2.56)*	1.79 (1.08-2.96)*	1.44 (0.84-2.49)
0.30–0.46	233	13	1.49 (0.93-2.39)	1.44 (0.84-2.47)	1.21 (0.67-2.17)
0.47–0.63	241	8	1.00 (0.58-1.71)	1.01 (0.55-1.85)	0.90 (0.47-1.72)
0.64–0.93	233	6	0.82 (0.46-1.48)	0.84 (0.43-1.64)	0.92 (0.47-1.83)
≥0.94	224	5	0.66 (0.34-1.28)	0.79 (0.38-1.61)	0.78 (0.36-1.69)
History of AIDS					
Yes	498	12	1.55 (1.03-2.34)*	1.54 (0.96-2.45)	1.33 (0.79-2.24)
No	708	7	0.95 (0.63-1.44)	1.12 (0.70-1.79)	1.04 (0.63-1.71)

[a]PR, prevalence ratio; CI, confidence interval.
[b]Multivariate model 1, referred to as the partially adjusted model, was generated using logistic regression to generate prevalence ratios. This model adjusted for age (at substudy visit), study site, distance of timed-gait test, race/ethnicity, baseline educational attainment, baseline depressive symptoms, baseline hepatitis C virus, baseline frequency of alcohol consumption, baseline income, baseline BMI, baseline marital status, baseline smoking history, and baseline HIV risk category.
[c]Multivariate model 2, referred to as the fully adjusted model, was generated using logistic regression. In addition to covariates listed in the partially adjusted mode1, the fully adjusted model included sociodemographic covariates collected at the substudy visit. These covariates included concurrent depression, concurrent frequency of alcohol consumption, concurrent income, concurrent BMI, concurrent marital status, and concurrent smoking history.
[d]AUC $CD4^+$, area under the curve; multivariate models were further adjusted for last $CD4^+$ count prior to HAART initiation.
[e]Concurrent ratio of $CD4^+/CD8^+$ is based on distribution of HIV-infected women.
*p values significant at $\alpha = 0.05$.

over time. Moreover, the role of cumulative antiretroviral therapy on physical functioning was not assessed as these investigations were beyond the scope of the current analysis. Although our measures establish a baseline to which future assessments can compare, our estimates should be viewed conservatively, as our WIHS comparison group reflects women who are closer in many characteristics to HIV-infected women but may not be representative of the general population. Notably, they suffered from high rates of severe depressive symptoms, obesity, and injection drug use.

For most women who had not experienced severe $CD4^+$ cell depletion, there did not appear to be any residual impairment in physical functioning relative to HIV-negative women. This positive conclusion will benefit from additional follow-up, particularly among WIHS participants entering older age groups. Our findings about HIV-positive women with the greatest $CD4^+$ cell losses and a history of HAART are important, given that care is often initiated late in the course of HIV disease, when $CD4^+$ cell counts are low.[40] Consistent monitoring of T cell lymphocyte subsets, even when counts fall below 200, should remain a vital component of clinical screening.[41] Further studies are necessary to elucidate the relationship between markers of HIV-related disease progression, chronic inflammation, and other measures of disease severity, such as weight loss, on the development and onset of disability and frailty,

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Disclosure Statement

The authors have no conflicts of interest to report.

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Address correspondence to:
Stephen J. Gange, Ph.D.
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 North Wolfe Street, Room E7638,
Baltimore, MD 21205

E-mail: sgange@jhsph.edu