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FRAILTY AND CONSTELLATIONS OF FACTORS IN AGING HIV-INFECTED AND UNINFECTED WOMEN - THE WOMEN'S INTERAGENCY HIV STUDY

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Abstract

Background—Biological similarities are noted between aging and HIV infection. Middle-aged adults with HIV infection may present as elderly due to accelerated aging or having more severe aging phenotypes occurring at younger ages.

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Objectives—We explored age-adjusted prevalence of frailty, a geriatric condition, among HIV + and at risk HIV− women.

Design—Cross-sectional.

Setting—The Women's Interagency HIV Study (WIHS).

Participants—2028 middle-aged (average age 39 years) female participants (1449 HIV+; 579 HIV−).

Measurements—The Fried Frailty Index (FFI), HIV status variables, and constellations of variables representing Demographic/health behaviors and Aging-related chronic diseases. Associations between the FFI and other variables were estimated, followed by stepwise regression models.

Results—Overall frailty prevalence was 15.2% (HIV+, 17%; HIV−, 10%). A multivariable model suggested that HIV infection with CD4 count<200; age>40 years; current or former smoking; income ≤$12,000; moderate vs low fibrinogen-4 (FIB-4) levels; and moderate vs high estimated glomerular filtration rate (eGFR) were positively associated with frailty. Low or moderate drinking was protective.

Conclusions—Frailty is a multidimensional aging phenotype observed in mid-life among women with HIV infection. Prevalence of frailty in this sample of HIV-infected women exceeds that for usual elderly populations. This highlights the need for geriatricians and gerontologists to interact with younger `at risk' populations, and assists in the formulation of best recommendations for frailty interventions to prevent early aging, excess morbidities and early death.

Keywords

Frailty; HIV; HCV; aging

Introduction

HIV infection continues to be a major global health issue affecting approximately 34 million people worldwide. With current therapies, HIV infection has evolved from a fatal infection, to a treatable, chronic condition of aging among older adults (1, 2). Over half of HIV-infected people in the United States (US) today are age 50 years and older (3). Yet, achieving 50 years with HIV infection does not denote onset of typical geriatric syndromes. Throughout adult life, HIV infection is synergistic with adverse aging influences on the immune, vascular, reproductive, and central nervous systems, thereby accelerating the aging process (4, 5). Evaluating these systems in middle-aged HIV infected women is essential to understanding HIV impact on aging.

Frailty is a clinical, geriatric syndrome consisting of multisystem dysregulation that increases vulnerability to various internal and external stressors, followed by loss of independence, disability, and mortality (6). Many definitions and indices of frailty exist (7, 8). The Fried Frailty Index (FFI) is most commonly used and considered to be a physical frailty index (9, 10). The FFI includes measures of gait speed, handgrip strength, body weight loss, physical activity and exhaustion. Tailored frailty indices are needed for

evaluating certain quality of life outcomes and/or populations living with certain diseases (10). A frailty index (FI) for individuals with chronic HIV infection would be useful, since HIV-infected adults are faced with earlier onset infection-related and aging-associated conditions that contribute to distinct, yet overlapping aging phenotypes.

A previous publication from the Women's Interagency HIV Study (WIHS) reported that frailty per the FFI manifests among 14% of women with HIV infection at the average age of 39 years (11). Herein, we operationalize the FFI similarly to the Multicenter AIDS Cohort Study (MACS), which is composed of HIV-positive and HIV-negative men (12–14). With an age range of 50–64 years, MACS observed a 12% frailty prevalence among HIV+ and 9% among HIV− men (12).

The goal of these WIHS analyses are to: 1) evaluate the complexity of frailty in women with versus without HIV infection through cross-sectional associations of HIV infection and the FFI, considering constellations of demographic and aging-related chronic disease factors; and 2) operationalize frailty for future age-matched comparisons between HIV infected women and men, as well as comparisons of frailty over time.

Methods

Study Population

WIHS is a prospective, observational cohort suitable to study the intersection of HIV-infection and aging. WIHS participants enrolled at six sites (Bronx/Manhattan, Brooklyn, Chicago, Los Angeles, San Francisco and Washington DC); methods and baseline cohort characteristics have been described previously (15). Participant enrollment occurred after approval by each site's institutional review board and the WIHS Executive Committee. All participants provided written informed consent. Participants engage in return visits every 6 months, which include an extensive face-to-face interview by trained interviewers, medical examinations, and laboratory specimen collection.

Inclusion criteria

When frailty measures were performed in 2005, there were 2305 HIV+ and at risk negative (HIV−) eligible women. Of these, 2018 (88%) adequately completed frailty measures. Since the FFI is comprised of five components (described below), participants had to have at least 3 of 5 frailty components measured for determination of the frailty phenotype to be included in this analysis.

Primary outcome

The FFI was defined according to well-described criteria (9). A woman was classified as frail if she exhibited three or more of five characteristics: 1) impaired mobility, 2) reduced grip strength, 3) physical exhaustion, 4) unintentional weight loss and 5) low physical activity. Mobility was measured using a 3–4 meter timed gait test, and impaired mobility was defined as the lowest quintile of performance by site among HIV negatives. Grip strength was measured using a dominant hand-held dynamometer with maximum force; reduced grip strength was the lowest quintile of performance by site among HIV negatives.

Physical exhaustion was a “Yes” to: “During the past four weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra efforts? Low physical activity was a “Yes” to “Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?” Unintentional weight loss was a “Yes” to: “Since your last visit, have you had unintentional weight loss of at least 10 pounds?”

Predictor variables

Our core predictors were HIV infection status and age. Methods for determining HIV and HCV infection status, Acquired Immunodeficiency Syndrome (AIDS) diagnosis, CD4 cell count, HIV viral load, antiretroviral therapy (ART) use, and intravenous drug use (IDU) were described previously (11). Several constellations of factors were also considered: demographic/health behavior and chronic aging-related disease variables.

Statistical analyses

For consistency of statistical methods used and data interpretation, all variables were considered as categorical. We used both crude and age-adjusted models to address the question of whether age is an important predictor of frailty in this middle-aged sample of HIV+ and HIV− women. Within each constellation described, stepwise regression models selected best predictors of the FFI. Best fit variables ($p<0.05$) in stepwise models were subsequently included in multivariable logistic regression models (and removed if $p>0.10$ later occurred) to obtain final models for each exposure constellation. Combined HIV status/CD4 count and age were core variables, and forced into each model. Finally, significant ($p<0.05$) variables identified from each constellation were combined into one final multiple logistic regression model for the prediction of frailty (FFI=3-5). Results of logistic regression models are presented as Odds Ratios (OR) with 95% Confidence Intervals (CI) and are considered significant at $p<0.05$. Data analyses were accomplished using SAS 9.3.

Results

Data were available on 1449 HIV+ and 579 HIV− women (average age 39 years). The prevalence of frailty was 15.2%, and more common among those with HIV infection compared to those without (17.3% vs 10.0%, $p<0.0001$). The average cutpoint for the lowest 20th%ile of grip strength was 23.15 kg; and for the highest 4m walking speed, 4.54s. Demographic/Health Behavior and Chronic Aging-related Diseases disease variables are presented in Table 1, based on HIV infection status, and presence of frailty. Almost 50% of HIV-infected were 40 years or older at the frailty assessment. The cross-sectional age-adjusted odds of frailty for Demographic/Health Behavior and Chronic Aging-related Diseases are presented in Table 2. The odds of frailty among HIV-infected increased with decreasing CD4 count. Among HIV-infected, frailty was positively associated with HIV viral loads >100,000 copies/ml, HCV co-infection, prior AIDS-defining illness, and ART use. Frailty was associated with increasing age; current or former smoking; IDU history, annual income less than $12,000; abstinence from alcohol; history of diabetes, cancer and

hypertension; and increasing FIB4 and decreasing eGFR. After age-adjustment, all of the aforementioned crude associations remained significant (P<0.05).

The HIV-frailty association was adjusted for the two constellations of factors in a series of models: Demographic/Health Behavior and Chronic Aging-related Diseases as presented in Table 3. Model 1, our basic model, shows that frailty was positively associated with age independently of HIV, despite the young age of the sample. Women age 50 years and older had over twice the odds of frailty as those age 30–39; and overall, age older than 50 years was most associated with frailty (OR 8.72, 95%CI 4.29–17.73). In addition, women with HIV infection were more likely to be frail than women without HIV infection, independent of age. This association was strengthened as CD4 count dropped, thus indicating an association between degree of immunosupression and frailty.

Adding various constellations of factors (models 2–3) that represent different aspects of aging and non-aging-associated vulnerability generally decreased the significance of the association of HIV infection with frailty, with and without consideration of CD4 count. Adding Demographic/Health Behavior variables (Model 2) to Model 1, showed that current or former smoking vs never smoking and annual income below poverty level (<$12 000), were independently moderately associated with frailty (69–83% higher odds). In this model, the risk ratio for HIV infection and CD4 count <200 cells/ml was similar to that in Model 1. Adding Chronic Aging-related Diseases variables to Model 1, showed that hypertension, FIB-4 >3.25 and eGFR less than 30 to 44.9 ml/min, compared to >60 ml/min, were associated with 2.7 to almost 4-fold higher odds of frailty.

Finally, in Model 4, all constellations of factors were included. HIV-infected with a CD4 count <200 cells/ml (vs HIV negative) had over a 2-fold higher odds of frailty, which is relatively modest compared to the 3.7-fold higher odds of frailty among those 50 years and older or with eGFR between 30-44.9 ml/min. Other factors that were significant, but had lower impact in terms of associated risk estimates were smoking, low income, and hypertension. The final model included representation from each constellation of factors, again emphasizing frailty as a syndrome, among women who are aging with a chronic infectious disease.

Discussion

The definition of frailty, a geriatric condition, is being evaluated in populations not traditionally at risk for aging-associated morbidities and co-morbidities, including middle-aged women with HIV infection (16, 17). As the world faces a growing number of people who are aging with chronic HIV infection, it becomes relevant to examine frailty at younger adult ages and the factors and outcomes associated with this multidimensional syndrome. A previous WIHS publication, reported that the frailty phenotype manifests among women with HIV infection even at the young average age of 39 years (11). We repeated this analysis using a different operationalization of the FFI, and to consider whether there are different constellations of factors that could be confounding or mediating this association among those with or at risk for HIV infection. Our analyses show that the frailty phenotype is associated with HIV-infection related sociodemographic factors, health behaviors, and

aging-related chronic diseases and comorbidities. This lends support to Rockwood's definition of frailty as an accumulation of deficits across multiple domains (18, 19). Among women with HIV infection, these analyses show that not only HIV and HIV markers, but also other modifiable factors, contribute to being frail. These results concur with a published comparison of 4 frailty scales, including FFI, which showed that the best tool to predict future risk of disability and mortality included a measure of frailty and a comorbidity measure (20).

The role of other infectious diseases, such as HCV, or associated markers of chronic kidney (low eGFR) and liver (moderate FIB-4) function, overwhelm associations with other morbidities in our analyses. As observed in the WIHS, approximately one quarter of those with HIV-infection in the US also have HCV infection (21). HIV and HCV co-infection leads to a general increased risk of morbidities and mortality (22, 23). Here we show that both HIV and HCV infection are associated with frailty, however in multivariable analyses the independent association of HCV infection disappears.

Kidney and liver function are also associated with both aging processes and HIV infection. eGFR, a marker of kidney function, tracks both progressive HIV infection and aging. It has been shown that among uninfected adults aged 70 years and older, almost 40% manifest an eGFR <60 ml/min; and most reductions are moderate (45–59 ml/min) (24). While a lower proportion with lower kidney function is observed here, it is associated with frailty. In this younger group of HIV infected or at risk women in the WIHS. It has been debated whether a moderately reduced eGFR is a marker of chronic kidney disease or associated with aging in individuals without HIV infection if few or no other morbidities are present (25). As the population of HIV survivors grows, impaired kidney function will become a growing public health issue. FIB-4 index >3.25, a marker of advanced liver fibrosis, was also associated with the FFI in 6.1% of HIV-infected and 2.5% of HIV-uninfected participants. As the FIB-4 index has not been validated in elderly (26), the overlap of reference values for older adults with HIV infection status are unknown. However, FIB-4 is a component of HIV-specific mortality indices, and given HCV co-infection, liver disease is a significant burden (27).

Typical aging-related comorbid conditions, such as hypertension, and factors such as income and smoking, while significant, were less important for frailty than HIV. The impact of aging-related comorbid conditions is anticipated to increase with advancing age. Thus, the `frailty profile' may change as HIV-infected and uninfected women age and develop other and more serious forms of aging-related co-morbidities. Overall, two factors, age 50 years or older (vs <30) and eGFR 30-44.9 ml/min, (vs >=60) had frailty OR >3 ($p<0.05$) in the final multivariable model. OR between 2 and 3 ($p<0.05$) were observed for age 30–49 years (vs < 30).

A limited number of studies have found that middle-aged HIV+ adults have a prevalence of frailty comparable to older uninfected counterparts (11–14, 28, 29). In studies of HIV-elderly, most frailty prevalence estimates are gathered among those age 65 years and older (8). In these samples, frailty prevalence is generally similar to that observed in these WIHS participants, average age 39. These analyses show, as others have (11–14), that frailty is a syndrome accelerated by HIV infection and other conditions that occur in HIV-infected and

at risk people. Frailty is multidimensional across domains and disease states even among women with an infectious disease that not long ago, was sure to lead to death.

Prefrailty (defined as an FFI of 2, 18% of WIHS participants in this analysis) was not considered as a separate outcome. Due to the younger age of our sample, uncertain etiology of the frailty phenotype in women with or at risk for HIV infection, desire for maximal comparability with the published literature, and associations with multiple constellations of factors, it was deemed most auspicious to focus on frail (FFI=3-5) vs non-frail (FFI=0–2) comparisons.

The strengths of the WIHS cohort include the comprehensive frailty assessment consistent with well-established criteria; extensive co-existing clinical, survey and laboratory assessments; and information on chronic aging-related morbidities. These strengths allow us to analyze broad constellations of factors related to aging-related hypotheses. There are also limitations. First, as a cross-sectional analysis, no conclusive statements can be made regarding cause and effect. Second, as frailty is measured at one point in time, incidence is unknown and it is unknown whether there is fluctuation, increase, or even regression, in frailty measures over time as other analyses have shown (12). A changing phenotype may be especially common in a younger sample of women at the beginning of the aging process when frailty criteria are met because of acute exposures versus chronic effects of aging. Third, our analyses use any and all available data at the FFI examination and as far back as two examinations prior if data are missing at the FFI visit. While it is a strength of these analyses to use previously collected data, it is a weakness due to the assumption that these retrospective data remain relevant at the time of the frailty measures. Fourth, a participant had to have measured at least 3 components of the FFI to be deemed frail, thus we may underestimate frailty in this sample. Finally, different frailty indices exist, as well as different ways to operationalize the FFI (7, 8). Thus slightly different estimates of frailty may be obtained.

Frailty is a highly relevant issue for aging HIV-infected or at risk women during mid-life. In these analyses, we began with the FFI, to which were added important co-morbidities representing constellations of Demographic/Health Behavior and Chronic Aging-related Diseases factors. As a result, we expand the field of Gerontology to include younger adults experiencing aging phenomena.

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Table 1

Characteristics of Women's Interagency HIV Study Participants by HIV Status

	HIV− N (%)	HIV+ N (%)	p
Fried Frailty Index (FFI)			
0–2	521 (90.0)	1199 (82.8)	<0.0001
3–5	58 (10.0)	250 (17.3)	
VACS Index			
Age group (years)			
Age < 30	130 (22.5)	112 (7.7)	<0.0001
Age 30–39	183 (31.6)	462 (31.9)	
Age 40–49	185 (32.0)	582 (40.2)	
Age 50+	81 (14.0)	293 (20.2)	
CD4 count (cells/mm^3)			
≥ 500		599 (41.4)	
200–499		630 (43.5)	
< 200		219 (15.1)	
Viral Load (copies/ml)			
< 500		852 (58.8)	
500–100,000		540 (37.3)	
>100,000		56 (3.9)	
FIB4			
< 1.45	523 (92.4)	1067 (74.1)	<0.0001
1.45–3.25	29 (5.1)	286 (19.9)	
> 3.25	14 (2.5)	88 (6.1)	
eGFR (ml/min)			
>=60	568 (98.3)	1337 (92.3)	<0.0001
45–59.9	5 (0.9)	73 (5.0)	
30–44.9	3 (0.5)	16 (1.1)	
< 30	2 (0.4)	22 (1.5)	
Hepatitis C Co-infection	90 (15.5%)	325 (22.4%)	0.0005
Race/Ethnicity			
White	109 (18.8)	336 (23.2)	0.0513
Black	373 (64.4)	854 (58.9)	
Others	97 (16.8)	259 (17.9)	
Education ≥High School	382 (66.2)	886 (61.3)	0.0384
Former/current smoking	426 (73.6)	999 (68.9)	0.0393
Income < $12,000	251 (45.0)	699 (50.0)	0.0465
Drinking			
Abstainer/None	231 (39.9)	773 (53.4)	<0.0001
Low	233 (40.2)	516 (35.6)	
Moderate	83 (14.3)	133 (9.2)	
High	32 (5.5)	27 (1.9)	

	HIV− N (%)	HIV+ N (%)	p
BMI ≥30 kg/m^2	270 (47.0)	487 (33.8)	<0.0001
HIV-related factors			
ART use		993 (68.6)	
Prior AIDS Defining Illness		602 (41.6)	
IDU	96 (16.6)	322 (22.4)	0.0042
Aging-Related Chronic Diseases			
HTN	168 (29.0)	443 (30.6)	0.4900
Diabetes	89 (15.4)	199 (13.7)	0.3399
Cancer	30 (5.2)	171 (11.8)	<0.0001

Table 2

Age-adjusted Odds of Frailty by Participant Characteristics

Variable	OR (95%CI)
HIV Status (cells/mm^3)	
Negative (Baseline)	reference
Positive CD4 ≥ 500	1.14 (0.79, 1.64)
Positive CD4 200–499	1.64 (1.16, 2.32)
Positive CD4 < 200	2.63 (1.74, 3.99)
Race/Ethnicity	
White	0.96 (0.70, 1.32)
Black	reference
Others	0.93 (0.67, 1.30)
Education ≥High School	0.72 (0.56, 0.93)
Current/former smoking	1.78 (1.29, 2.45)
Income < USD$12,000	1.92 (1.48, 2.49)
Intravenous Drug Use (IDU)	1.63 (1.23, 2.16)
Drinking	
Abstainer/None	reference
Low	0.63 (0.47, 0.84)
Moderate	0.54 (0.34, 0.87)
High	1.20 (0.61, 2.33)
BMI ≥ 30kg/m^2	0.91 (0.70, 1.18)
HIV-related factors (HIV+ only)	
ART use	1.44 (1.04, 1.99)
Viral Load (copies/ml)	
< 500	reference
500–100,000	1.28 (0.96, 1.72)
>100,000	2.60 (1.40, 4.82)
CD4 (cells/mm^3)	
≥ 500	reference
200–499	1.53 (1.16, 2.02)
< 200	2.45 (1.72, 3.50)
Prior ADI	2.35 (1.75, 3.16)
Chronic Disease-Related Factors	
HTN	1.65 (1.27, 2.16)
Diabetes	1.52 (1.11, 2.08)
Cancer	1.48 (1.03, 2.12)
FIB4	
< 1.45	reference
1.45–3.25	1.68 (1.22, 2.31)
> 3.25	3.24 (2.07, 5.06)
eGFR (ml/min)	

Variable	OR (95%CI)
≥ 60	reference
45–59.9	1.54 (0.91, 2.60)
30–44.9	4.63 (1.80, 11.95)
< 30	3.98 (1.74, 9.13)

Table 3

Cross-Sectional Multivariate Logistic Regression Models with Frailty (FFI=3–5) as outcome

Variable	Model 1*	Model 2	Model 3	Model 4
HIV and CD4 count (cells/mm^3)				
Negative	reference	reference	reference	reference
Positive CD4 ≥ 500	1.14 (0.79, 1.64)	1.16 (0.80, 1.70)	1.15 (0.79, 1.69)	1.17 (0.79, 1.74)
Positive CD4 200–499	1.64 (1.16, 2.32)	1.63 (1.13, 2.33)	1.59 (1.10, 2.29)	1.61 (1.10, 2.36)
Positive CD4 < 200	2.63 (1.74, 3.99)	2.56 (1.67, 3.94)	2.08 (1.33, 3.28)	2.07 (1.29, 3.31)
Age group (years)				
Age < 30	reference	reference	reference	reference
Age 30–39	2.48 (1.21, 5.09)	2.32 (1.12, 4.79)	2.23 (1.08, 4.60)	2.13 (1.02, 4.43)
Age 40–49	4.53 (2.25, 9.11)	3.54 (1.74, 7.18)	3.53 (1.74, 7.18)	2.86 (1.39, 5.88)
Age 50+	8.72 (4.29, 17.73)	6.38 (3.10, 13.10)	4.84 (2.29, 10.21)	3.71 (1.74, 7.92)
Smoking		1.83 (1.30, 2.58)		1.67 (1.18, 2.36)
Income < $12K		1.69 (1.30, 2.21)		1.65 (1.26, 2.17)
Drinking				
Abstainer/None		reference		reference
Low		0.70 (0.52, 0.95)		0.72 (0.53, 0.97)
Moderate		0.51 (0.32, 0.83)		0.46 (0.28, 0.77)
High		1.09 (0.55, 2.16)		1.07 (0.53, 2.19)
Hypertension			1.61 (1.22, 2.13)	1.67 (1.25, 2.23)
FIB4				
< 1.45			reference	reference
1.45–3.25			1.37 (0.98, 1.92)	1.31 (0.93, 1.84)
> 3.25			2.49 (1.55, 4.00)	2.27 (1.39, 3.69)
eGFR (ml/min)				
≥ 60			reference	reference
45–59.9			1.32 (0.77, 2.28)	1.33 (0.76, 2.32)
30–44.9			3.70 (1.42, 9.61)	3.74 (1.37, 10.22)
< 30			2.71 (1.12, 6.54)	2.36 (0.94, 5.95)

Results are presented as OR (95%CI);

* Model 1 includes HIV variables and age; Model 2: Model 1 + demographic variables; Model 3: Model 1 + Chronic Aging Diseases variables; Model 4: Model 1 + Model 2 + Model 3