AIDS PATIENT CARE and STDs
Volume 25, Number 1, 2011

DOI: 10.1089/apc.2010.0242

Association of Age and Comorbidity with Physical Function in HIV-Infected and Uninfected Patients: Results from the Veterans Aging Cohort Study

Krisann K. Oursler, M.D., Sc.M.,[1] Joseph L. Goulet, Ph.D., Sc.M.,[2] Stephen Crystal, Ph.D.,[3] Amy C. Justice, M.D., Ph.D.,[2] Kristina Crothers, M.D.,[4] Adeel A. Butt, M.D., M.S.,[5] Maria C. Rodriguez-Barradas, M.D.,[6] Knachelle Favors, M.H.,[1] David Leaf, M.D.,[7] Leslie I. Katzel, M.D., Ph.D.,[1,8] and John D. Sorkin, M.D., Ph.D.[1,8]

Abstract

HIV clinical care now involves prevention and treatment of age-associated comorbidity. Although physical function is an established correlate to comorbidity in older adults without HIV infection, its role in aging of HIV-infected adults is not well understood. To investigate this question we conducted cross-sectional analyses including linear regression models of physical function in 3227 HIV-infected and 3240 uninfected patients enrolled 2002–2006 in the Veterans Aging Cohort Study-8-site (VACS-8). Baseline self-reported physical function correlated with the Short Form-12 physical subscale ($\rho = 0.74$, $p < 0.001$), and predicted survival. Across the age groups decline in physical function per year was greater in HIV-infected patients (β_{coef} −0.25, $p < 0.001$) compared to uninfected patients (β_{coef} −0.08, $p = 0.03$). This difference, although statistically significant ($p < 0.01$), was small. Function in the average 50-year old HIV-infected subject was equivalent to the average 51.5-year-old uninfected subject. History of cardiovascular disease was a significant predictor of poor function, but the effect was similar across groups. Chronic pulmonary disease had a differential effect on function by HIV status ($\Delta\beta_{coef}$ −3.5, $p = 0.03$). A 50-year-old HIV-infected subject with chronic pulmonary disease had the equivalent level of function as a 68.1-year-old uninfected subject with chronic pulmonary disease. We conclude that age-associated comorbidity affects physical function in HIV-infected patients, and may modify the effect of aging. Longitudinal research with markers of disease severity is needed to investigate loss of physical function with aging, and to develop age-specific HIV care guidelines.

Introduction

Evidence for increased risk of age-associated conditions in HIV-infected patients, including coronary artery disease and cardiovascular risk factors,[1–4] chronic pulmonary disease,[5–7] low bone mineral density,[8] and frailty[9] supports the concern that chronic HIV infection and prolonged antiretroviral therapy might be associated with an accelerated aging process.[2,5,7,10,11] In adults without HIV, history of these age-associated conditions is an independent risk factor for decline in physical function with aging.[12–16] The purpose of this study was to investigate the effect of age-associated conditions on physical function in HIV-infected patients compared to uninfected patients with similar demographic characteristics and medical care setting. Prior to combination antiretroviral therapy (cART) physical function in HIV-infected patients was studied in younger adults with AIDS.[17] Limitation with activities of daily living (ADL) was common,

[1]University of Maryland School of Medicine, Veterans Affairs Maryland Healthcare System, Baltimore, Maryland.
[2]Yale University School of Medicine and Public Health, Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut.
[3]Center for Health Services Research on Pharmacotherapy, Chronic Disease Management, and Outcomes, Institute for Health, Rutgers University, New Brunswick, New Jersey.
[4]University of Washington, Seattle, Washington.
[5]University of Pittsburgh School of Medicine, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania.
[6]Michael E. DeBakey VA Medical Center, Department of Medicine, Baylor College of Medicine, Houston, Texas.
[7]UCLA School of Medicine, Greater Los Angeles Veterans Affairs Healthcare System Los Angeles, California.
[8]Baltimore Veterans Affairs Medical Center Geriatric Research, Education, and Clinical Center, Baltimore, Maryland.

and was associated with leg muscle atrophy and weakness in the setting of AIDS wasting syndrome.[18] Research in the cART era shows that ADL capacity is preserved in more than 90% of the HIV-infected patients, but these patients remain limited in vigorous activities (exercise, walking hills, heavy work).[19,20] The prevalence of age-associated conditions, such as chronic lung disease and coronary artery disease, was associated with decreased self-reported physical function in a 2001–2002 cross-sectional study of 889 HIV-infected and 647-uninfected veterans.[20] Association of the conditions with function was independent of age, race, and smoking history and was not affected by HIV status. However, only 88 (10%) of the HIV-infected patients were 60 years of age and older. We hypothesized that older HIV-infected patients would have greater limitations in function compared to older uninfected patients, and that this effect would be amplified by cardiac and pulmonary disease. We conducted a cross-sectional study to investigate the relationship of self-reported physical function with prevalent age-associated conditions defined by ICD-9 codes at the baseline visit for HIV-infected and -uninfected patients enrolled in the Veterans Aging Cohort Study- 8 site (VACS-8), an ongoing longitudinal study.[21] Mortality data currently available during follow-up were used to test construct validity of function survey items.

Methods

VACS-8 participants are enrolled prospectively from eight VA Medical Centers and include patients with HIV infection followed in infectious disease clinics, and age and race group-matched uninfected patients followed in general medicine clinics.[21] All participants provided written informed consent for the protocol, which is approved by the respective Institutional Review Board (IRB) and VA research and development committees at each site. Enrollment began in 2002 and is ongoing. Patients provide information on physical activity, smoking, alcohol use, illicit drug use, health-related quality of life (SF-12), and demographic characteristics at study entry and then yearly. Clinical and administrative data are abstracted from the VA electronic medical record using methodology validated by chart review[21] (details available, www.vacohort.org). Comorbid conditions are defined by ICD-9 diagnostic codes and require at least one inpatient or two outpatient encounters within 12 months prior to or 6 months after study enrollment to be considered present at baseline.[22] For this analysis comorbid conditions were chosen based on available ICD-9 data, and plausible relationship with physical function in HIV-infected patients[20] and uninfected patients.[12] For instance, despite the increased risk of low bone mineral density[8,23] and certain cancers in HIV-infected patients, and the probable impact on function, these conditions were not included since VACS-8 data are not yet available. Patients were classified with chronic obstructive lung disease if they had a diagnosis of chronic obstructive pulmonary disease (COPD; including ICD-9 codes for bronchitis and emphysema) or asthma, based on VACS research focused on obstructive lung disease and relationship to smoking and mortality.[24,25] The analytic set includes baseline data collected from 2002–2006 in 3227 HIV-infected patients and 3240 uninfected patients. Only 213 individuals were excluded because of incomplete survey items for physical function. In the HIV group CD4 cell count, HIV-1 viral load, and hemoglobin concentration at baseline were available for 90% of the patients.

Physical function was quantified using the VACS function scale, a measure derived by summation of patient report on 12 questions included in the VACS-5 survey[20] and originally adapted from the HIV Cost and Services Utilization Study (HCSUS; available online, www.vacohort.org). The questions span the continuum from basic activities of daily living (feeding, bathing, and dressing one's self) to instrumental activities of daily living (light, moderate, and heavy types of work), mobility (walking a few steps, walking inside, and walking one block) and vigorous activity (walking uphill, running, sports). Patients report their current ability to perform each physical activity. For analysis of VACS-8 data, we refined the previously used scale[20] to facilitate comparison with physical function scales in the HIV literature.[26,27] First, we scored the items so that higher numbers represented greater capability to perform the activity (unable to do = 0, yes but slowly = 1, yes = 2). Then, we transformed the raw scale to a scale of zero to 100 by dividing the sum by the maximum possible score (24) and multiplying by 100. The interitem consistency of the scale and domains were tested using Cronbach α and factor analysis. To assess the content validity we tested the VACS function scale and the physical component scale of the SF-12 by Spearman's ρ. To assess construct validity, we performed survival analyses to determine whether baseline physical function measured by the VACS function scale predicted death through the most recent follow-up visit.

Differences in clinical characteristics between HIV-infected and uninfected patients were assessed using log-linear models adjusted for demographic factors after initial univariate comparisons by t-test or chi-squared test. The function scale was used as the main outcome measure in linear regression models. Parallel models stratified by HIV status tested the association of function with independent variables (demographics, lifestyle factors, comorbidity) for each patient group. Differences in the β coefficient of the independent variables between HIV-positive and HIV-negative models were tested using a z statistic. To test for effect modifiers, independent variables that were significantly different ($p < 0.05$) in the stratified analysis were included in a single combined multivariable model with all subjects and an HIV-interaction term. In order to provide a clinical context for the impact of effect modifiers (x), age equivalent function in an uninfected subject was calculated for a 50-year-old HIV-infected subject. First we computed the predicted function in HIV-infected subjects alone ($\gamma_{HIV} = \beta_0 + \beta_1 age + \beta_2 x$) using age = 50 years. Then using this function outcome (y_{HIV}) we solved for age of uninfected subjects using coefficients derived from the model in uninfected subjects alone.

Cox regression was used to test the association of mortality with baseline physical function, categorized as impaired (lowest tertiary, score < 67), moderate limitations (score 67–99), and no limitations (score = 100). Eight subjects did not have any follow-up data. The remaining subjects were included in the survival analysis that included event data through follow-up visit 4. Subjects were censored at the date of their last survey. Cox proportional hazards models were tested for proportionality assumption and were valid. Significance was defined as a two-tailed α of 0.05.

Results

Study population

The age distribution was similar in HIV-infected and uninfected patients (mean years ± standard deviation [SD], 49.5 ± 8.7 versus 50.7 ± 10.0). Differences in lifestyle factors and comorbid conditions between groups adjusted for demographic factors (age, race, gender) are summarized in Table 1. HIV-infected patients reported exercising less frequently than uninfected patients ($p = 0.03$). When this analysis was stratified by age, exercise frequency remained lower among older HIV-infected patients (age ≥ 55 years, $p = 0.05$), but was similar between younger HIV-infected and uninfected patients (age ≤ 44 years, $p = 0.1$).

Function scale

Factor analysis showed that the VACS physical function scale had a single domain with high degree of interitem consistency (Cronbach $\alpha = 0.9$). A ceiling effect was present; 35% of the subjects reported no limitations in physical activities (score of 100). The VACS physical function score correlated with the SF-12 physical subscale ($\rho = 0.74$ $p < 0.001$), which was unchanged when stratified by HIV group. Physical function score (adjusted mean ± standard error [SE]), was significantly higher in patients who exercised weekly 5 or more times (86.0 ± 0.8), 3–4 times (85.0 ± 0.7), 1–2 times (81.8 ± 0.8), and less than once (77.0 ± 0.8) compared to patients who never exercised (68.0 ± 0.9; all $p < 0.001$). The median follow-up time was 5.2 years (interquartile range [IQR] 4.2–5.7 years). During this time, 560 (18.0%) of the HIV-infected patients and 232 (7.4%) of the uninfected patients died. Patients with functional impairment (those scoring below 67, lowest tertile) had a two-fold increased risk of death compared to patients without any functional impairment (score = 100), adjusted for effects of demographic and baseline clinical characteristics (Table 2).

HIV infection, age, and physical function

There was no significant difference in the mean physical function score between HIV-infected patients (mean ± SD; 82.6 ± 0.4) and uninfected patients (82.4 ± 0.3). In the combined multivariable model including demographic and clinical factors for all subjects, physical function was significantly lower in HIV-infected patients compared to uninfected patients, but the effect was very modest (β_{HIV} −1.3, 95% confidence interval [CI] [−2.3, −0.2] $p = 0.02$). In the stratified HIV model higher HIV-1 viral load ($\log_{10}$ copies per milliliter) was associated with worse function but the effect was small and did not remain significant in the multivariable model (Table 3). Patients with a hemoglobin ≤ 12 g/dL had on average a 7-point lower score than those with higher hemoglobin. Patients who were within 180 days of starting combination antiretroviral therapy (cART, 3 or more antiretroviral medications) at baseline had worse function compared to patients not receiving cART. However, there was no significant difference for patients who had been on cART for greater than 180 days.

The decline in physical function score associated with each additional year of age was three times greater for HIV-infected patients (β_{HIV+} −0.25, 95% CI [−0.33, −0.17]) compared to uninfected patients ($\beta_{HIV-} = -0.08$, 95% CI [−0.16, −0.01]; Table 4). Stratified analysis by age group

Table 1. Description of Study Population by Demographic and Clinical Characteristics

Characteristic	*HIV uninfected* N = *3147* n	*% Total*	*HIV infected* N = *3107* n	*% Total*	p *Value*[a]
Age, years					
≤ 44	785	25.0	849	27.3	<0.001
45–49	699	21.3	728	23.4	
50–54	701	22.3	696	22.4	
≥ 55	992	31.5	834	26.8	
Gender, male	2897	92.1	3028	97.5	<0.001
Race					
Black	1951	62.0	2070	66.6	<0.001
White	776	24.7	625	20.1	
Hispanic	313	10.0	295	9.5	
Other	107	3.4	117	3.8	
Lifestyle factors:					
Weekly exercise[b]					0.03
Never	330	10.5	395	12.8	
< 1 times	569	18.2	526	17.1	
1–2 times	831	26.5	759	24.7	
3–4 times	781	24.9	822	26.7	
≥ 5 times	623	19.9	575	18.7	
Body mass index (BMI, kg/m^2)					<0.001
Underweight (BMI < 18.5)	38	1.2	106	3.4	
Normal (BMI 18.6–24.9)	703	22.5	1446	46.9	
Overweight (BMI 25.0-29.9)	1225	39.2	1149	37.3	
Obese (BMI ≥ 30)	1161	37.1	380	12.3	
Smoker, current	1380	43.8	1,650	53.1	<0.001
Substance abuse[c]					
History of alcohol disorders	724	23.0	583	18.7	<0.001
History of injection drug use	483	15.5	1032	33.6	<0.001
Comorbidity:					
Congestive heart failure	105	3.3	61	2.0	<0.001
Coronary artery disease	318	10.1	158	5.1	0.006
Diabetes	716	22.8	397	12.8	<0.001
Hepatitis C	482	15.3	968	31.2	<0.001
Hypertension	1668	53.0	933	30.0	<0.001
Major depression	465	14.8	420	13.5	0.3
Chronic pulmonary disease[d]	351	11.2	295	9.5	0.2
Peripheral vascular disease	116	3.7	60	1.9	0.003
Stroke	119	3.8	66	2.1	0.001

[a] p Value for difference between HIV-uninfected and HIV-infected patients, χ^2 tests used for demographic characteristics, log linear regression models adjusted for demographics used for lifestyle and clinical characteristics.

[b] How often engage in regular activities (e.g., brisk walking, jogging, etc.) long enough to work up a sweat?

[c] History of alcohol disorders by ICD-9 codes; Injection drug use, prior self-reported use.

[d] Pulmonary disease included chronic obstructive pulmonary disease (bronchitis and emphysema) or asthma.

Table 2. Baseline Physical Function Independently Predicts Mortality

Physical function at baseline	Total N	Death				
			Unadjusted		Adjusted[a]	
		N (%)	HR	95% CI	HR	95% CI
No limitations (score = 100)	2217	169 (7.6)	1.0		1.0	
Intermediate limitations	2535	327 (12.9)	1.68	1.40, 2.03	1.37	1.13, 1.65
Severe limitations (score < 67, lowest 20%)	1494	296 (19.8)	2.67	2.21, 3.22	1.96	1.60, 2.39
Total	6246	792 (12.7)				

[a]Adjusted for demographic characteristics, baseline lifestyle factors, and comorbid conditions.
HR, hazard ratio; CI, confidence interval.

and HIV status showed better function in the younger (≤44 years) HIV-infected patients compared to the uninfected ($p < 0.01$), and worse function in the older (>55 years) HIV-infected patients compared to the uninfected ($p < 0.01$; Fig. 1). Although the HIV-age interaction was statistically significant (HIV*age ß$_{coeff} = -0.17$, $p < 0.01$), function differences were small. In terms of equivalent years without adjustment for comorbidity, the average 50-year-old HIV-infected subject had the same level of function as the average 51.5-year-old uninfected subject.

Comorbid conditions and physical function

HIV-infected and uninfected patients with a history of cardiovascular disease, including congestive heart failure, coronary artery disease, peripheral vascular disease, and stroke had on average function scores 9–12 points lower than patients without the condition (Table 4). Diagnosis of hypertension was significantly associated with worse physical function controlled for demographic factors (β_{HTN} −2.8, 95% CI [−3.9, −1.8]) but was no longer significant in the multivariable model. These relationships were similar in HIV-infected and uninfected patients.

Table 3. Association of Physical Function with HIV-Related Factors Based on a Multivariable Linear Regression Model Including Demographic and Clinical Variables Listed in Table 1

Characteristic	N	b	95% CI	p Value
CD4 count:				
≤200 cells/mm^3	687	−2.6	−5.0, −0.2	0.03
201–500 cells/mm^3	1338	0.5	−1.3, 2.4	0.6
>500 cells/mm^3	880	—	—	—
HIV-1 RNA, per log$_{10}$ copies/mL	2535	−0.05	−0.75, 0.66	0.8
Hemoglobin				
≤12 gm/dL	444	−4.9	−7.2, −2.6	<0.001
>12 gm/dL	2470	—	—	
cART history in prior year:				
Cumulative use, days				
None	525	—	—	—
1–180	622	−3.4	−6.07, −0.67	0.02
181–364	1001	−1.7	−4.21, 0.71	0.1
365	801	−1.2	−3.94, 1.46	0.4

cART, combination antiretroviral therapy; CI, confidence interval.

The independent effect of the history of chronic obstructive lung disease on function was greater in HIV-infected patients (Fig. 2). Physical function adjusted for demographic, lifestyle, and comorbidity factors was comparable in HIV-infected and uninfected patients without pulmonary disease across all age groups. However, among patients with pulmonary disease, HIV-infected patients had significantly worse function compared to uninfected patients; a 50-year old HIV-infected subject had the equivalent level of function as a 68.1-year old uninfected subject. These results were confirmed in the full multivariable model; the interaction term for HIV and pulmonary disease was significant (HIV*pulmonary ß$_{coeff} = -3.6$, 95% CI [−6.6, −0.4], $p = 0.03$).

Obesity, based on body mass index (BMI) ≥ 30, was associated with poor function in uninfected patients but not in HIV-infected patients (Table 4). Being underweight (BMI < 18.5) was associated with poor function in HIV-infected patients, but not in uninfected patients. However, these differences in the relationship of BMI group and function by HIV status were small and were not statistically significant (Table 4).

Among HIV-infected patients, history of diabetes was not associated with function when adjusted for effect of BMI and comorbidity (Table 4). However, in uninfected patients diabetes was significantly related to function. This differential effect of diabetes on function by HIV status was statistically significant, and reflected the finding that a 50-year-old diabetic HIV-infected subject had the equivalent level of function as a 36-year-old diabetic uninfected subject.

Discussion

In this cross-sectional study we compare physical function of HIV-infected patients to uninfected patients who are demographically similar and under care in the same medical system. The baseline function score, based on patient reported ability to perform a range of physical activities, correlates with the established SF-12 physical subscale, and is associated with differential survival. The majority of patients in this clinic-based cohort are 50 years of age and older in both patients groups, a frequently used benchmark to designate older HIV-infected adults. This opportunity allowed us to investigate the relationship of age and function with comorbidity between HIV-infected and uninfected patients.

Within the limits of a cross-sectional study, the difference in function between younger and older patients was greater in HIV-infected patients compared to the uninfected patients, adjusted for comorbidity. The magnitude of the rate of decline

Table 4. Multivariable Linear Regression Models of Physical Function in HIV-Infected and Uninfected Subjects

	HIV uninfected N = *3126*			*HIV infected* N = *3081*			*Difference (HIV infected-uninfected)*		
	b	*95% CI*	p *Value*	*b*	*95% CI*	p *Value*	*Delta*	*SE*	p *Value*[a]
Age, per year	−0.08	(−0.16, −0.01)	0.03	−0.2	(−0.33, −0.17)	< .0001	−0.17	0.06	< 0.01
Gender, female	−1.4	(−3.87,1.14)	0.29	−4.7	(−8.97, −0.35)	0.03	−3.30	2.54	0.19
Race									
Black	1.4	(−0.19,3.01)	0.09	0.8	(−1.01,2.54)	0.40	−0.64	1.22	0.60
Hispanic	−0.2	(−2.67,2.27)	0.87	−2.7	(−5.34,0.03)	0.05	−2.45	1.86	0.19
Lifestyle factors:									
Body mass index (BMI, kg/m^2)									
Underweight (BMI < 18.5)	−1.8	(−7.89,4.26)	0.56	−6.2	(−9.99, −2.41)	< 0.01	−4.39	3.65	0.23
Overweight (BMI 25.0–29.9)	0.5	(−1.26,2.24)	0.58	1.3	(−0.21,2.78)	0.09	0.79	1.17	0.50
Obese (BMI ≥ 30)	−2.6	(−4.39, −0.73)	0.01	−0.9	(−3.12,1.38)	0.45	1.69	1.48	0.25
Current smoker	−4.0	(−5.4, −2.51)	< 0.0001	−2.4	(−3.8, −0.96)	< 0.01	1.58	1.03	0.13
History of alcohol disorders	0.6	(−1.1,2.39)	0.47	−1.4	(−3.28,0.48)	0.14	−2.04	1.31	0.12
Comorbid conditions:									
Congestive heart failure	−6.1	(−9.95, −2.32)	< 0.001	−9.5	(−14.49, −4.51)	< 0.001	−3.37	3.20	0.29
Coronary artery disease	−5.6	(−8, −3.29)	< 0.0001	−7.8	(−10.99, −4.53)	< .0001	−2.11	2.04	0.30
Diabetes	−5.2	(−6.88, −3.56)	< 0.0001	−1.8	(−3.88,0.38)	0.11	3.47	1.37	0.01
Hepatitis C	−2.2	(−4.08, −0.26)	0.03	−3.8	(−5.37, −2.25)	< 0.0001	−1.64	1.26	0.19
Hypertension	−1.6	(−3.04, −0.1)	0.04	−0.02	(−1.65,1.61)	0.98	1.55	1.12	0.17
Major depression	−8.2	(−10.14, −6.32)	< 0.0001	−4.9	(−6.97, −2.85)	< 0.0001	3.32	1.44	0.02
Pulmonary disease[b]	−3.8	(−5.9, −1.69)	< 0.0001	−7.3	(−9.61, −4.93)	< 0.0001	−3.48	1.60	0.03
Peripheral vascular disease	−6.7	(−10.28, −3.18)	< 0.01	−7.2	(−12.22, −2.13)	0.01	−0.44	3.15	0.89
Stroke	−6.3	(−9.85, −2.83)	< 0.001	−6.7	(−11.49, −1.97)	0.01	−0.39	3.02	0.90

[a]p value between groups.
[b]Pulmonary disease includes chronic obstructive pulmonary disease (bronchitis and emphysema) or asthma.
Reference groups: white race, normal BMI (18.6-24.9), former/never smoker, and for each comorbidity, patients without the condition based on ICD-9 codes.
CI, confidence interval.

in function across the age groups was greater in the HIV-infected patients. In both the 50–54 and 55 + age groups physical function was worse in the HIV-infected patients. These results are supported by exercise performance testing that shows significantly lower aerobic capacity among older HIV-infected patients compared to age-matched uninfected adults.[28] It should be noted in the younger (age ≤ 44 years) age group that HIV-infected patients reported higher function than uninfected patients. Only this age group of HIV-infected patients had similar frequency of exercise compared to the uninfected patients. This finding raises the question of the role of physical inactivity in worse physical function among older HIV-infected patients.

In the general medical literature, poor physical function is strongly associated with cardiovascular disease (CVD), including coronary artery disease, congestive heart failure, peripheral vascular disease, and stoke.[12,13,15,16] For all of these conditions we found a significant independent association

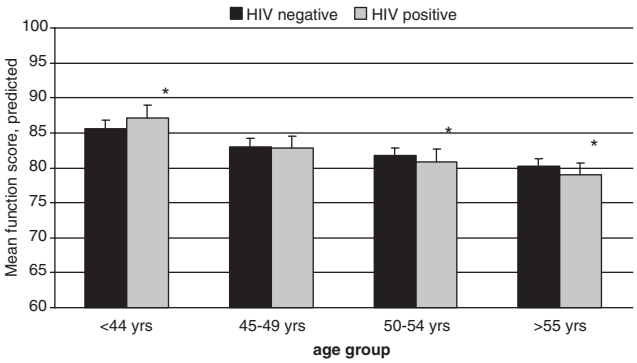

FIG. 1. Mean (standard error [SE]) of predicted physical function score by HIV status and age group based on multivariable models. *$p < 0.05$.

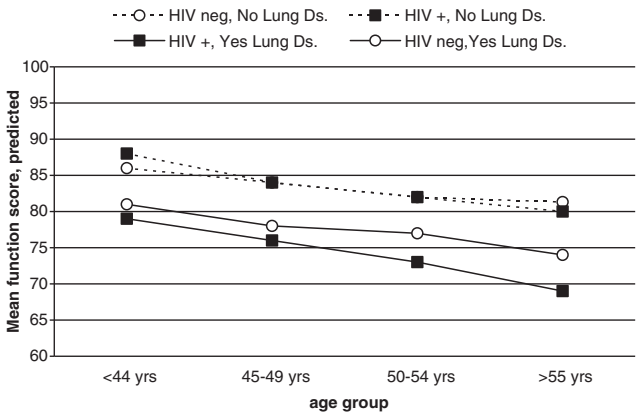

FIG. 2. Mean predicted physical function score by HIV status for patients with and without lung disease (lung ds.) by subject age group based on multivariate models.

with function in HIV-infected patients that was similar to uninfected patients. Given that HIV-infected patients may have increased risk of coronary heart disease and cardiac dysfunction,[1,3,29] CVD will likely become a significant source of physical disability in HIV-infected patients who are otherwise stable on cART, and thus provides additional incentive to reduce cardiac risk factors.[4] Although none of the CVD conditions in our study were associated with worse function in HIV-infected patients compared to uninfected patients, our function scale may be unable to distinguish these differences given the scale's ceiling effect. In addition, self-report in general may be limited in its capacity to measure specific functional performance parameters, such as endurance, which are related to cardiovascular disease. For instance, exercise treadmill testing has shown that aerobic capacity is reduced 16% in older HIV-infected men with hypertension compared to those without hypertension.[30] Further research is needed to investigate the specific mechanisms underlying poor function for different types of CVD, and whether differences exist between HIV-infected and uninfected patients.

In contrast, the VACS function score clearly showed an additive effect of chronic obstructive lung disease and HIV on physical function. The results were consistent across the age groups with adjustment for other comorbid conditions and smoking history. Chronic pulmonary disease is independently related to functional limitations in uninfected adults,[31,32] and may occur more frequently in HIV-infected adults.[5–7] Our results suggest that among those with chronic obstructive lung disease, HIV-infected patients have worse physical function compared to uninfected patients. However, conclusions should be tempered given the lack of information on lung function. Physical function in HIV-infected patients among those with chronic pulmonary disease could be worse due to either accelerated progression[33] or longer duration of lung disease. A third possibility is a confounding factor related to both chronic pulmonary disease and function. Recent research shows that the adjusted risk of lung cancer, pulmonary hypertension and pulmonary fibrosis is greater in HIV-infected compared to uninfected patients.[6] Although these conditions may be less common, they are associated with chronic lung disease and were not considered in our analyses. While understanding these mechanisms is beyond the scope of this study, the results support an HIV aging interaction driven by comorbidity that warrants further investigation. With regard to HIV care, this finding supports the importance of smoking cessation.[24,34]

Finally, the contrasting results for BMI and diabetes in HIV-infected versus uninfected patients highlights the challenge of differentiating effects of medication, HIV infection, and aging. HIV-infected patients classified as obese by BMI likely represent a heterogeneous group, which includes those experiencing a restoration to health phenomenon that comes with successful antiretroviral therapy. This supposition is supported by the Nutrition for Healthy Living study, a prospective longitudinal study that showed that HIV-infected men with a five kilogram or larger increase in total body weight reported improvement in physical function.[26] Importantly, HIV-infected individuals have experienced the effects of obesity for a shorter period of time than uninfected subjects since they were likely thinner prior to receiving cART treatment. The attenuated negative association of diabetes with function in the HIV-infected group supports this possibility. However, our findings are limited without data on duration or severity of diabetes, and need to be investigated further. In addition, anthropometrics may provide information that is missed by measure of BMI alone.[35]

Our findings confirm that advanced HIV disease is associated with worse physical function. However, in comparison to earlier studies which focused on the effect of AIDS on function,[17] the majority of HIV-infected VACS participants receive cART and have high CD4 cell counts. Our findings demonstrate that age-related comorbidity should be considered an important risk factor for poor physical function in this clinical setting. For example, history of congestive heart failure is independently associated with a 10-point lower function score, compared to a low CD4 cell count (<200 cells/cm^3), which is associated with a 3-point lower score. Unlike our preliminary study,[20] in this larger cohort with over 1450 patients with hepatitis C infection, the relationship between hepatitis C and function was similar in HIV-infected and uninfected patients (Table 4). The absence of a significant interaction was confirmed in the full multivariable model (HIV*HCV $ß_{coeff} = -1.7$, $p = 0.1$). However, further work is needed to investigate this relationship as we defined hepatitis C infection by ICD-9 code and did not differentiate cases by ongoing viral replication, nor severity of liver disease.

The primary limitation of the study is related to the cross-sectional design. We report a decline in function with age that that compares individuals at different ages, not a within-person difference in rate of decline. Therefore, findings could reflect selection or cohort effects, and require confirmation in longitudinal analysis. An additional limitation is the definition of comorbid conditions by history only, without data on disease severity and duration. While most cross-sectional studies are limited to prevalent cases, it is possible that duration and severity of some comorbid conditions may be greater in HIV-infected patients and then translate to worse function. Self-reported limitations in physical activities allow for measure of function within the social context, but can be affected by reporting bias. This may be evident given the large proportion of patients that denied any physical limitations. Although this ceiling effect is very similar to a survey study on function in community dwelling HIV-infected patients,[26] it limits the ability to investigate higher level of functioning. While the study results are subject to these limitations in terms of causal inference, they provide important direction for future research in aging and physical function.

In summary, age-associated comorbidity affects physical function in HIV-infected patients. Longitudinal research with measure of disease incidence and severity is needed to determine if there is an accelerated loss of function with aging. However, our results highlight the potential role of comorbidity as an effect modifier in the relationship of HIV and aging. The study supports further integration of primary health care and prevention into HIV care with increased focus on age-associated comorbidity.[36]

Acknowledgments

Supported by the National Institutes of Health (NIH) K23AG024896 (K.K.O.); U01AA13566 (A.C.J.); R01HL090342 (K.C.); R01MH058984 (S.C.); University of Maryland Claude

D. Pepper Older Americans Independence Center P60AG 028747 (K.K.O., L.I.K., J.D.S., K.F.), and Department of Veterans Affairs Baltimore Geriatric Research, Clinical and Education Center (L.I.K., J.D.S.).

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Krisann K. Oursler, M.D., Sc.M.
Department of Medicine
University of Maryland School of Medicine
10 North Greene Street
BVAMC
Baltimore, MD 21201-1524

E-mail: koursler@grecc.umaryland.edu