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Accelerated Longitudinal Gait Speed Decline in HIV-Infected Older Men

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Conflicts of interest:

None of the authors has an association that may pose a conflict of interest for the present work.

Abstract

Background: Gait speed predicts functional decline, disability, and death and is considered a biomarker of biological aging. Changes in gait speed in persons aging with HIV may provide an important method of gauging health and longevity in an under assessed population. The objective of this study was to evaluate and quantify the rate of gait speed decline in HIV infected (HIV+) men compared to HIV uninfected (HIV-) men.

Methods: The study was nested in the Multicenter AIDS Cohort Study (MACS). The primary outcome was usual gait speed in meters per second (m/s) measured between 2007 and 2013. Differences in the rate of gait speed decline and the incidence of clinically slow gait (<1.0 m/s) were assessed using multivariate linear regression models and Cox proportional hazards models, respectively.

Results: A total of 2,025 men (973 HIV+ and 1,052 HIV-) aged 40 and older contributed 21,187 person-visits (9,955 HIV+ and 11,232 HIV-) to the analysis. Average gait speeds at age 50 years were 1.24 m/s and 1.19 m/s in HIV- and HIV+ men, respectively ($p < 0.001$). In fully adjusted models, gait speed decline averaged 0.009 m/s per year after age 50 ($p < 0.001$); this decline was 0.025 m/s per year greater in HIV+ men ($p < 0.001$). Moreover, HIV+ men had a 57% greater risk of developing clinically slow gait (aHR=1.57, 95% CI: 1.27 – 1.91).

Conclusions: These findings indicate a faster rate of functional decline in HIV-infected men, suggesting greater risks of disability and death with advancing age.

Key words: gait speed, HIV-infection, functional decline, disability, aging

Introduction

Over 1.1 million people living in the United States are HIV-infected (HIV+)[1]. Due to highly active antiretroviral therapy (HAART), those living with HIV now have the potential to live a long life[2]; however, the long-term consequences of treated HIV infection on health and quality of life are unknown. It has been postulated that HIV infection may lead to an accelerated aging phenotype regardless of HIV virologic suppression[3], due to a pro-inflammatory state[4] and greater comorbidity burden present in those aging with HIV[5-7]. As life expectancy of those living with HIV continues to increase[8], these factors may contribute to an accelerated rate of functional decline and disability.

Slow gait speed is a well-established predictor of functional decline, disability, and death in older adults[9-11]. It has been associated with clinical progression of several chronic diseases in the general population, including diabetes, dementia, and congestive heart failure[12], and has been proposed as a method to distinguish between normal and pathological aging[13]. Among HIV+ persons, slowed gait and an increased risk of poor functional performance have been observed compared to HIV- populations [14-17], yet larger sample sizes, a control group of similar HIV- adults, and longitudinal data are needed to better describe the trajectory of functional decline, and the risk of poor functional performance, by HIV status. Moreover, until recently the HIV+ population has not been old enough to observe the onset and trajectory of the age-related decline in gait speed.

Given the established prognostic power of gait speed[11, 12, 18], a systematic examination of the onset and rate of gait speed decline in a large population of HIV+ middle- and older-aged adults, relative to HIV- adults of similar demographics and lifestyle behaviors, may help define whether those living with HIV experience accelerated aging[19]. Therefore, the purpose of this study was to test the hypothesis that HIV+ persons experience earlier and faster gait speed decline than HIV- persons. To this end, we analyzed gait speed measurements collected over a 6-year period in the Multicenter AIDS Cohort Study (MACS), an ongoing study of the history of HIV infection that includes HIV+ and HIV- men who have sex with men (MSM).

Methods

Study Population

The MACS includes over 7,000 HIV+ and demographically similar HIV- MSM enrolled in Baltimore/Washington, Chicago, Los Angeles, and Pittsburgh/Ohio in 1984–1985 (n=4,954), 1987–1991 (n=668), 2001–2003 (n=1,350), and 2010-2013 (n= 17). Specific details of the study have been published[20]. Briefly, participants complete semiannual study visits consisting of a standardized interview, physical examination, lifestyle questionnaires, and collection of blood for laboratory testing and storage. Informed consent is obtained from all study participants, and the institutional review boards at each study site approved the study protocol.

On October 1, 2007, the MACS began measuring gait speed at each study visit as part of a frailty assessment. The current study includes 2,025 MACS participants aged 40 years or older at baseline who contributed longitudinal gait speed assessments between October 1, 2007 and September 30, 2013. Baseline was defined as the first study visit at which a participant's gait speed was measured.

Gait speed

Gait speed was assessed over a 4-meter course in the clinic corridor. Participants were asked to walk at their "normal, comfortable pace." Timing was initiated with a command of "Go" and stopped after the first foot-fall over the finish line. Two measurements were conducted, with the faster used for analysis.

HIV status

All men were assessed for HIV positivity by ELISA and confirmed by Western blot. For HIV- men, HIV status was assessed at each study visit.

Covariates

Date of birth, race, and education were self-reported at enrollment. Cigarette smoking, drug use, and comorbidities were self-reported at each study visit during the analysis period. For analyses, smoking and drug use were dichotomized as "ever" or "never." Race was dichotomized into white (non-Hispanic) or non-white. Education was defined as: (i) less than high school, (ii) high school or high school and some college,

or (iii) college degree or more. Hepatitis C infection was defined by detectable hepatitis C RNA in serum; and hepatitis B infection was defined by positive hepatitis B surface antigen. Mental health was assessed using the mental component summary (MCS) score of the SF-36, and was dichotomized as < or > 42 for the analysis[21]. Height and weight were measured using standard procedures, and body-mass index (BMI) was calculated as [mass (kg)] / [height (m)]^2. Hypertension was defined as systolic pressure > 140 mm Hg, diastolic pressure > 90 mm Hg, or self-reported diagnosis of hypertension with use of antihypertensive medications. Diabetes mellitus was defined as fasting glucose > 126 mg/dL or self-reported previous diagnosis with use of diabetes medication. Liver disease was defined as current or past medical records confirmed diagnosis of liver disease not including infection with hepatitis B virus or hepatitis C virus. Arthritis was defined as prior or current self-reported arthritis pain. Peripheral neuropathy was defined as current or past report of pain, burning, numbness, or pins and needles sensation in the feet or legs, or measured inability to detect a vibratory sensation in either foot.

T-lymphocyte subsets were measured at each MACS visit using standardized 3-color flow cytometry[22]. Plasma HIV RNA concentrations (viral load) were measured using the Roche ultrasensitive assay (limit of detection = 50 copies/mL; Roche Diagnostics, Nutley, NJ). HAART was defined according to the U.S. Department of Health and Human Services Kaiser Panel guidelines[23] as three or more antiretroviral drugs including either: (i) a protease inhibitor; (ii) a nonnucleoside reverse transcriptase inhibitor; (iii) an entry or integrase inhibitor; or (iv) three nucleoside reverse transcriptase inhibitors, including abacavir or tenofovir. AIDS was defined using the Centers for Disease Control and Prevention's 1993 definition, excluding cases defined only by a CD4 T-cell count <200 cells/ul[24], and confirmed by review of medical records.

Statistical Analysis

Two-sample t-test and chi-square test statistics were used to evaluate differences in continuous and categorical variables by HIV status, respectively. Exploratory data analyses included locally weighted regression smoothers, box plots, quadratic fit plots, and histograms to assess the normality of the gait speed distribution.

Based on these results, the longitudinal association between continuous gait speed and age was modeled using generalized linear models with generalized estimating equations (GEE) and an exchangeable working correlation matrix to take into account correlation of repeated measures of gait speed from individuals. Combined (Table 2) and HIV-stratified models (Table 3) were created to assess differences in the rate of change in gait speed by HIV status. Covariates included age (centered at 50), weight, height, race, education, smoking status, MCS score, history of drug and alcohol use, diabetes, liver disease, hypertension, arthritis, peripheral neuropathy, hepatitis B, and hepatitis C. The model restricted to HIV+ men (Table 3), included HIV viral load (<200 vs. >=200 copies/ml) [25], nadir CD4 T-cell count, and history of AIDS. Variables included in the final models were restricted to those with statistical significance ($p < 0.05$).

Kaplan-Meier survival estimates and adjusted Cox proportional hazard models were used to estimate differences in time from age 40 to slow gait by HIV status. Slow gait was defined as <1.0 m/s as this threshold has been associated with increased risk of mobility disability, hospitalization, and death in the general aging population[10]. Separate analyses of HIV+ men were performed to assess differences between those with and without slow gait by exposure to "d-drugs" (didanosine, stavudine), AZT (zidovudine), and efavirenz, and by time on HAART, using analyses of variance with Tukey-Kramer pairwise comparisons and pairwise logistic regression models. In additional analyses, use of these drugs was compared among three groups of HIV+ men: (i) those who never had slow gait, (ii) those who had slow gait at baseline, and (iii) those with incident slow gait during the study. All analyses were conducted using Stata SE version 13 (Statacorp, College Station, TX).

Results

The study population consisted of the 2,025 men (973 HIV+ and 1,052 HIV-) aged 40 and older who had two or more study visits between October 1, 2007 and September 30, 2013. These men contributed 21,187 person-visits (9,955 HIV+ and 11,232 HIV-) to the analysis. The mean number of visits per participant was 10.2 (range: 2-17) for HIV+ men and 10.7 (range 2-17) for HIV- men (p=0.35). Baseline characteristics of these men are shown in Table 1. HIV+ participants were on average 3.4 years younger than HIV- participants and had lower BMIs (p-values <0.001); and HIV+ participants were more likely to have liver disease, peripheral neuropathy, hepatitis B, and hepatitis C infection, be non-white, report a history of drug use, and have fewer years of education, and were less likely to consume alcohol (p-values <0.001). There was a wide range of gait speeds, from less than 0.14 m/s to more than 1.9 m/s (supplemental Figure 1), which is consistent with previous studies[12, 26].

Figure 1 displays the unadjusted mean and 95% confidence interval association between age and gait speed by HIV status using a quadratic fit plot. Gait speeds were similar by HIV status among those aged 40-49, but after age 50 there was clear separation between the HIV- and HIV+ men, as indicated by the non-overlapping confidence intervals of the respective curves, with unadjusted gait speed at age 50 averaging 1.24 m/s in HIV- participants and 1.19 m/s in HIV+ participants (p <0.001). In the fully adjusted model including HIV+ and HIV- men (Table 2), gait speed declined 0.009 m/s for each one-year increase in age after age 50 (p <0.001). There was a significant negative association with HIV status, in which gait speed declined 0.025 m/s more per year in HIV+ men, on average, than in HIV- men (p <0.001). Further, the interaction between age and HIV status was also significant (β= -0.002 m/s, p= 0.007), indicating that the magnitude of the difference between HIV+ and HIV- men increased with age. Other significant predictors of gait speed included: weight, height, race, education, hepatitis C status, and peripheral neuropathy. There was no interaction between race and peripheral neuropathy or education. Smoking, history of drug and alcohol use,

diabetes, liver disease, hypertension, arthritis, MCS score, and hepatitis B infection were not significant and were not included in the final model.

In analyses stratified by HIV status, there were strong negative associations between gait speed and age in both the HIV+ (β = -0.012 m/s per year, $p < 0.001$) and HIV- (β = -0.011 m/s per year, $p < 0.001$) groups (Table 3). Height, weight, race, education, and peripheral neuropathy contributed significantly to both HIV+ and HIV- models, but hepatitis C infection was significant only in the HIV- model. In the HIV+ model, there was a significant association between nadir CD4 T-cell count and gait speed decline (β = 0.002 m/s per year for each 50 cell/ul increase, $p = 0.029$), but suppressed viral load (<200 copies/ml) did not have a significant effect.

To provide clinical perspective, we examined the effect of HIV status on the time to development of slow gait speed (<1.0 m/s). As shown in Figure 2, the trajectories of time to slow gait were significantly different between HIV+ and HIV- men ($p < 0.001$), with 50% of the HIV+ men exhibiting slow gait by age 57 compared to age 66 among the HIV- men. In Cox proportional hazard models using age as the time metric and adjusting for the variables that were significant in the continuous analysis (height, weight, race, education, peripheral neuropathy, and hepatitis C), the hazard of developing slow gait was 57% greater for HIV+ compared with HIV- men (aHR 1.57; 95% CI, 1.27 – 1.91).

To examine the potential effects of treatment on the risk of slow gait, HIV+ men were stratified into three groups: (i) those who never had slow gait, (ii) those who had slow gait at baseline, and (iii) those who had incident slow gait during the study. There were no meaningful or statistically significant differences among these groups by cumulative years on HAART or by cumulative years on ddI, d4T, AZT, or efavirenz.

Discussion

The capacity to walk independently is a central component of independent living and essential to maintaining quality of life. To our knowledge, this study is the first to evaluate age-related gait speed decline prospectively in a large HIV+ population and compare these observations to a demographically similar HIV- population. In the general aging population, it has been suggested that a change in gait speed of 0.05 m/s or more is clinically meaningful[27]. In the current study, gait speed at age 50 was on average 0.05 m/s slower among HIV+ men compared to HIV- men, suggesting that a clinically meaningful difference in speed by HIV status exists in middle age. Moreover, the significant interaction between HIV and age indicate that the rate of gait speed decline intensifies with age among those with HIV. Overall, these results strongly support the hypothesis that HIV+ individuals experience earlier and faster gait speed decline than their HIV- peers.

Multiple factors have been associated with gait speed decline including decreased aerobic capacity, changes in body composition, threats to biomechanics (e.g., arthritis, balance difficulty), and compromised energy utilization[28-30], signifying that slowed gait speed is a reflection of underlying biological and physiological challenges that develop with age. A typical 65-year-old lives with two or more comorbid conditions[31]. The addition of chronic HIV infection to this comorbidity burden adds another layer of complexity to an aging system, even among the virologically controlled.

Although a link between reduced functional performance and HIV infection has been hypothesized, the majority of previous research has focused on the syndrome of frailty[32, 33], or on composite measures of performance[15, 34]. Richert, et al[16] analyzed gait speed over 10 meters, along with the five times sit-to-stand test and six-minute walk distance, in 354 middle-aged HIV+ participants (median age at baseline 46 years) and compared it to published data from the general aging population. After a two-year follow-up period, findings included greater deterioration in the five times sit-to-stand test and six-minute walk distance, but no difference in median 10-meter gait speed. In a study of injection drug users, Greene et al[17] found that after five years of follow-up, HIV+ participants had reduced physical performance and greater risk of mortality

than HIV- participants, but the rate of decline was not quantified or compared. The current study demonstrates a statistically significant difference in the trajectory of gait speed decline between men aging with HIV and demographically similar HIV- men. Given the increased risk of frailty and comorbidity burden that has been noted in those aging with HIV[32, 35, 36], this raises the concern that greater morbidity and disability among those aging with HIV may be forthcoming.

Gait speed declined significantly faster in non-white men than in white men, and this was true for both HIV+ and HIV- participants. This difference could not be explained by HIV infection, education, or peripheral neuropathy. Race-related differences in functional and mobility decline in the general aging population have been reported. In the Health, Aging and Body Composition study older blacks showed higher rates of mobility loss than whites, with greater risk of developing mobility limitations over follow-up even after accounting for poor mobility at baseline[37]. The mechanism of these differences is not known, but is generally believed to be related to life-long differences in socio-economic status[37, 38].

It is unclear from the current results how long-term antiretroviral treatment may affect gait speed decline. This is an important question, as nearly all of the HIV+ men in this study were receiving HAART, and the vast majority were virologically suppressed, characteristics which are likely to be similar in most populations aging with HIV. In the present study, analyses of HIV+ men with and without slow gait at baseline, or with incident slow gait, yielded no evidence that cumulative exposure to specific antiretroviral drugs (ddI, d4T, AZT, efavirenz) was associated with slower gait speed. These findings should be replicated in other, more diverse populations with greater power to detect differences by treatment. Moreover, the association between lower nadir CD4 cell count and faster decline in gait speed is consistent with previous research linking HIV with frailty[32, 33, 39] and underscores the importance of early initiation of therapy, and maintaining virologic suppression and sufficient CD4 cell count, particularly with advancing age.

The development of age-related chronic diseases in people with chronic HIV infection may be driven by a state of chronic inflammation. Although not having data on inflammatory markers is a limitation, stored samples will provide opportunities for future research. The negative association between hepatitis C and gait

speed among the HIV- participants may in part be explained by increased inflammatory burden, and also warrants future investigation.

The current study also was limited in its ability to assess the effect of HIV status on gait speed decline in those over age 65. As of September 2013, 24% of HIV- MACS participants were 65 or older and 11% were 70 or older. Among HIV+ participants, the corresponding figures were 9% and 3%. However, given the separation of the gait speed trajectories at age 50 and the steeper rate of decline among the HIV+ observed in this study, it is likely that the negative association between HIV infection and decline in gait speed would be amplified with advancing age. Future analyses of this cohort as it continues to age will help confirm this hypothesis.

The HIV+ men in the MACS may not be generalizable to other aging HIV+ populations, as longstanding participants of HIV cohort studies are likely to be different from the general HIV+ population. Moreover, 9% of MACS participants are age 65 or older compared with 5% of persons living with HIV in the United States[40], and many of these participants survived a period of time without effective treatment (i.e prior to 1996) and/or exposure to less effective and more toxic ART regimens, before achieving virologic suppression. Our results do not show a difference in gait speed and disability by experiences prior to effective treatment (specifically by d-drug usage); if there is, however, an unmeasured effect, the difference in gait speed and disability by HIV status may decrease in an era of effective, accessible treatment and ART initiation at higher CD4 counts. Further, the current study did not include women, limiting its generalizability to women aging with HIV.

As the treatment of HIV expands globally, the need to manage and treat age-related conditions in persons living with HIV will grow exponentially. The 57% increased hazard of developing slowed gait holds significant implications for the care of those aging with HIV+ who may be at increased risk of lower extremity limitations, hospitalization, and death. Accordingly, efforts to prevent and treat mobility loss in those aging with HIV should be a major public health focus. Given recent evidence from the general population, promoting physical activity and a healthy lifestyle are the best current options[41].

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Author contributions:

Study design: JBM, LPJ, JP, SK, BDJ, KME, TTB, JAS. Participant recruitment: JBM, LPJ, JP, SK, BDJ. Data analysis and results interpretation: JAS, KNA, LPJ, JBM, LF. Drafted manuscript: JAS. Critical Review: JBM, LPJ, JP, SK, BDJ, KME, LF, TTB. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest:

None of the authors has an association that may pose a conflict of interest for the present work.

Figure Legend:

Figure 1:

Quadratic fit plot of the unadjusted association (mean and 95% C.I.) between gait speed (m/s) and age (years) by HIV status.

Figure 2:

Kaplan-Meier estimates of the proportion of participants with gait speed > 1.0 m/s by years of age (x-axis), stratified by HIV status (log rank to compare survival distributions $p < .001$). The adjusted hazard ratio was derived from Cox proportional hazards regression models detailed in the Methods and Results sections.

Table 1: Baseline characteristics of study participants October 1, 2007 – September 30, 2013 (N=2,025), shown as mean and standard deviation (continuous variables) or number and percent (categorical variables).

	HIV+ n = 973		HIV- n = 1,052		
	Mean, n	**(SD) / %**	**Mean, n**	**(SD) / %**	**p-value**
Age (years)	48.7	(6.9)	52.1	(8.3)	<.001
Body Mass Index (kg/m^2) [a]	25.5	(4.1)	27.3	(5.2)	<.001
Non-white[b]	387	39.8%	259	24.6%	<.001
College Education[c]	449	46.1%	643	61.1%	<.001
Smoking[d]	236	24.3%	288	27.4%	.20
History of drug use[e]	484	49.8%	457	43.4%	.004
Alcohol use[f]	3.1	6.8%	5.2	9.6%	<.001
Diabetes[g]	125	12.8%	103	9.8%	.05
Liver disease[h]	37	3.8%	3	<1.0%	<.001
Hypertension[i]	400	41.6%	429	40.7%	.85
Arthritis[j]	30	3.1%	38	3.7%	.49
Peripheral neuropathy[k]	329	33.8%	233	22.2%	<.001
SF36 MCS[l]	49.9	(11.6)	49.9	(12.1)	1.00

Hepatitis B infection[m]	40	4.1%	7	<1.0%	<.001
Hepatitis C infection[n]	151	15.5%	94	8.9%	<.001
Gait speed at age 50 (m/s)	1.19	(0.04)	1.24	(0.01)	<.001
Years since seroconversion[o]	11.7	(8.2)			
Years of HAART[p]	7.3	(3.1)			
CD4 nadir (cells/ul)[q]	309	(209.9)			
Suppressed viral load[r]	629	66.2%			

[a] BMI, body mass index, calculated as weight in kilograms divided by height in meters squared

[b] Black (non-Hispanic), Black Hispanic, American Indian or Alaskan Native, Asian or Pacific Islander, other Hispanic, or other

[c] Completed college degree or more

[d] Current or former smoker

[e] History of any drug use

[f] Number of drinks per week

[g] Fasting glucose > 126 mg/dL or diagnosed with diabetes and use of medications

[h] Current or past confirmed diagnosis of liver disease

[i] Systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg or diagnosed with hypertension and use of medications

[j] Current or past report of arthritis pain

[k] Current or past report of pain, burning, numbness, or pins and needles sensation in the feet or legs, or measured inability to detect vibratory sensation in either foot

[l] Short form 36 mental component summary score

[m] Positive hepatitis B surface antigen

[n] Detectable hepatitis C RNA in serum

[o] Reported years from HIV diagnosis

[p] Reported years from HAART initiation

[q] Lowest CD4 T-cell count, as measured or reported and confirmed with medical records

[r] < 200 copies HIV RNA/ml

Table 2: Continuous, longitudinal association between age and gait speed, adjusted for HIV serostatus and other confounding variables, from October 1, 2007 – September 30, 2013 (N=2,025)

Dependent Variable: Gait speed (m/s)			
Independent variables:	**Coefficient**	**S.E.**	**p-value**
Age (per year centered at 50 years)	-0.009	.001	<.001
HIV infection	-0.025	.007	0.001
HIV* Age (per year centered at 50 years)	-0.002	.001	0.001
Weight (per kg)	-0.001	.0002	<.001
Height (per cm)	0.003	.001	<.001
Non-White Race	-0.084	.009	<.001
Education (years)	0.061	.006	<.001
Hepatitis C	-0.012	.004	.005
Peripheral neuropathy	-0.014	.003	<.001

Table 2 shows the final longitudinal model assessing the associations among age, HIV, and gait speed decline. Smoking, history of drug and alcohol use, diabetes, liver disease, hypertension, arthritis, mental quality of life, and hepatitis B were not significant and were not included in the final model.

Table 3: Continuous, longitudinal association between age and gait speed stratified by HIV status. October 1, 2007 – September 30, 2013 (N=2,025)

	HIV+			HIV-		
Dependent variable: Gait Speed (m/s)	**n = 973**			**n = 1,052**		
Independent variables:	**Coefficient**	**SE**	**p-value**	**Coefficient**	**SE**	**p-value**
Age (centered at 50 years)	-0.012	.0005	<.001	-0.011	.0005	<.001
Height (per cm)	0.002	.0001	.001	0.003	.0001	<.001
Weight (per kg)	-0.0007	.0003	.01	-0.001	.0002	<.001
Non-White Race	-0.073	.011	<.001	-0.099	.013	<.001
Education	0.058	.009	<.001	0.062	.009	<.001
Hepatitis C	-0.010	.006	.10	-0.014	.005	.02
Peripheral neuropathy	-0.016	.004	<.001	-0.012	.004	.01
CD4 nadir (per increase of 50 cells/ul)	0.002	.001	.03			
Suppressed viral load [a]	-0.007	.005	.15			

[a] Viral load <200 HIV RNA copies/ml