

Research Article

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Ambulatory Function in Men with and without HIV Infection: Association with Cardiorespiratory Fitness

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Abstract

Objective: The study purpose was to compare ambulatory function in men with and without HIV infection, and test the association with aerobic exercise capacity.

Methods: We conducted a cross-sectional study of 45 HIV-infected men and 37 age and race-matched HIV-uninfected men at the Baltimore VA Medical Center. Participants performed cardiorespiratory exercise testing, six-minute walk (6-MW) and the 400-meter long distance corridor walk (LDCW) as part of a study of veterans without history of cardiovascular disease.

Results: The mean (SD) age was 55 (6) years. Among the 82 male participants, 98% were African American race. The 6-MW distance correlated with aerobic exercise capacity (VO₂peak) in both HIV-infected subjects ($r=0.50$, $p<0.001$) and uninfected subjects ($r=0.57$, $p<0.001$). Duration in the 400 meter LDCW inversely correlated with VO₂peak in HIV-infected ($r=-0.52$, $p<0.001$) and uninfected subjects ($r=-0.48$, $p<0.001$). In linear regression models the variance in VO₂peak explained by the endurance walk test was similar for the 6-MW and LDCW across HIV groups (all $p>0.1$). Between HIV groups, there was a significant difference in LDCW ($p=0.01$) but not in 6-MW ($p=0.3$). Conclusions: In HIV-infected men without known CVD the 6-MW and LDCW provide similar estimates of aerobic exercise capacity. The findings are comparable to uninfected men with similar demographic and clinical characteristics, and support endurance walk tests to estimate aerobic exercise capacity in HIV-infected patients.

Keywords: HIV; Ambulatory Function; Cardiorespiratory fitness

Introduction

Ambulatory function predicts mortality and mobility disability in older adults [1-6]. However, little information is available in HIV-infected adults despite that fact that an estimated half of the HIV-infected individuals living in the United States will be 50+ years of age in the next five years [7]. Ambulatory function measured by self-paced walking tests assesses both mobility and capacity to perform real-life daily activities in adults with a wide range of limitations. Longer distance tests, such as the six-minute walk (6-MW) and the long-distance corridor walk (LDCW), correlate with aerobic exercise capacity (VO₂peak) measured by cardiorespiratory testing in patients with congestive heart failure [5] and chronic obstructive lung disease (COPD) [8]. These tests are therefore referred to as endurance walk tests to differentiate them from short-distance timed walks (e.g., 4-meter) that focus on mobility limitations and gait speed. Short-distance timed walks are also associated with leg strength [9], but are more likely to be limited by a ceiling effect in individuals with high level of physical function.

Richert et al. recently reported poor performance in the six-minute walk (6-MW) in a quarter of 324 HIV-infected adults (median age 48 years) based on normative data, generated by Enright's reference equation using age, sex, weight, and height [10]. Esposito and colleagues found the 6-MW distance to be 5% lower than expected in 27 younger men [11] using the same reference equation [12]. We reported a 8% lower 6-MW distance in 32 older HIV-infected men and a moderate correlation between the 6-MW distance and VO₂peak [13]. Erlandson et al. recently showed a 62% agreement between the LDCW and

short physical performance battery (SPPB) in assessment of physical function, but did not include exercise testing [14]. These studies are limited by lack of a HIV uninfected comparison group.

Compared to endurance walking tests, cardiorespiratory testing offers the advantage of precise physiologic data with information on degree of effort and workload. Oxygen utilization at peak exercise (VO₂peak) is a gold standard for aerobic exercise capacity and is significantly impaired in HIV-infected adults [15], which is associated with increased age [13], hypertension [16], hyperlactatemia [17], and low CD4 cell count [18]. However, cardiorespiratory testing requires expensive equipment and specially trained staff.

In contrast to the endurance walk tests, performance in short-distance timed walks in HIV-infected adults on successful antiretroviral therapy (ART) is not different from uninfected adults. The Women's Interagency HIV Study (WIHS) reported that the median time to complete the 4-meter walk test was similar in HIV-negative women

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Received March 29, 2013; Accepted May 10, 2013; Published May 18, 2013

Citation: Beans J, Stevenson T, Katzel LI, Sorkin JD, Warner AL, et al. (2013) Ambulatory Function in Men with and without HIV Infection: Association with Cardiorespiratory Fitness. J AIDS Clinic Res S9: 003. doi:10.4172/2155-6113.S9-003

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(4.24 secs) and HIV-infected women with CD4⁺ counts ≥ 500 cells/mm³ (4.28 secs) [19]. The corresponding gate speed, greater than one meter/sec, in these middle-aged women (median age 38 years (HIV -) and 41 years (HIV +)) is higher than threshold values for frailty in elderly women [20] and cut-off values that predict mortality [21] and mobility disability [1] in cohorts of uninfected elderly adults. However, WIHS HIV-infected women with CD4 cell count <100 cells/mm³ did meet these criteria with a significantly longer 4-meter walk test (5.08 secs) [19].

Ambulatory function is a feasible and validated geriatric construct, which can be used to investigate risk for physical disability, and all cause mortality in older HIV-infected adults. Current evidence in HIV-infected adults on successful ART suggests a deficit in walking endurance rather than mobility. Our study objective was to perform endurance walk tests in men with and without HIV infection, and test the association with aerobic exercise capacity.

Methods

Subjects

Men enrolled in the Veterans Aging Cohort Study (VACS) at the Baltimore VA Medical Center were recruited for the Cardiovascular Sub-study (CVD-VACS), which included cardiorespiratory testing and assessment of physical function. VACS is a multicenter prospective longitudinal observational study of HIV-infected veterans from HIV Clinics with age, race, and site group matched HIV uninfected veterans from General Medicine Clinics [22]. The CVD-VACS study excluded VACS participants with known cardiovascular disease (CVD), specifically: 1) history of prevalent coronary artery disease (myocardial infarction, angioplasty, stent placement, coronary artery bypass surgery or angina symptoms requiring medication); 2) history of peripheral vascular disease with claudication; 3) history of cerebral vascular disease (stroke or transient ischemic attack); and 4) stage 3 or 4 congestive heart failure. Participants with severe musculoskeletal disease, which required assist device for ambulation, were also excluded for safety reasons. Among the first 84 Baltimore site CVD-VACS participants, an endurance walking test was not completed in two subjects, with a resulting analytic set of 82 participants (45 HIV-infected, 37 uninfected participants). Participants provided written informed consent for both VACS and CVD-VACS, which were approved by the University of Maryland Baltimore Institutional Review Board and Baltimore VA Research and Development Committees.

Ambulatory function

The six-minute walk (6-MW) and long distance corridor walk (LDCW) tests were performed in random order on the same day in a corridor with pre-measured courses marked with cones. Sitting heart rate and blood pressure were measured immediately before and after each test. The second test followed the first after the participant's heart rate returned to its resting rate. Pulse oximetry and heart rate were not monitored while the participant walked. For the six-minute walk (6-MW) participants were instructed to cover as much distance as possible in six minutes by walking laps over a 100-foot course, based on the American Thoracic Society protocol [23]. Encouragement was limited to time splits: the time remaining after each minute and when subjects had 30 and 10 seconds remaining. Distance was measured to the nearest foot and then converted to meters. For the long distance corridor walk (LDCW) test subjects first completed a 2-minute warm up prior to the 400-meter timed walk [24]. The subjects were instructed to walk 10 laps around a 40 meter course marked by cones as quickly as possible

without running. Encouragement was limited to laps completed and laps remaining. Time to walk the 400 meters was measured in minutes and seconds with a stopwatch.

Cardiorespiratory exercise testing

Subjects performed cardiorespiratory exercise testing (CPET) on a motorized treadmill using the modified Bruce protocol with open circuit spirometry to measure gas exchange (oxygen and carbon dioxide) [15]. The modified Bruce protocol starts at a speed of 1.7 mph and 0% incline with workload increasing at standardized three minute intervals, incline only initially, then by both incline and speed. The test was terminated according to American College of Sports Medicine (ACSM) safety criteria [15] or when subject reported volitional exhaustion. Oxygen utilization, carbon dioxide production, and minute ventilation values were collected breath-by-breath with a Quark CPET and averaged at 10-second intervals. Peak oxygen utilization (VO_{2peak}) was calculated as the average of the highest three 10-second interval measurements near test termination.

Clinical and survey data

The VACS coordinating center provided clinical information on past medical history based on the electronic medical record as previously described [22], which was confirmed by history and physical exam on enrollment into CVD VACS. Data on cigarette smoking and illicit drug use was obtained from the annual VACS participant survey. During the research visit, current medication list was reviewed, height and weight were measured and used to calculate body mass index (BMI). Estimated 6-MW distance was calculated based on the formula for men by Enright ($1140 - 5.61(\text{BMI}) - 6.94(\text{age})$) [12].

Statistical analyses

Differences in subject characteristics and physical function in the HIV-infected and uninfected groups were determined by Student's t-test or chi-squared test. Pearson's correlation and linear regression models tested the association between VO_{2peak} and performance in the 6-MW and LDCW. Separate analyses were performed for the HIV-infected and uninfected subjects. The square root of the mean square error (RMSE), a measure of variance in the dependent variable adjusted for the independent variable, was calculated for each bivariate model. Differences in slopes (beta coefficients) and RMSE between models were tested using the F-statistic. Analyses were performed with STATA statistical software (Stata 9.0; STATAcorp, College Station, TX).

Results

The majority of HIV-infected subjects were receiving combination antiretroviral therapy with a non-detectable HIV-1 viral load (<400 copies/ml) in 91% and a high CD4 cell count (median (IQR): 445 (265-531)). There was no difference in age between the HIV-infected and uninfected men (mean \pm SE, years: 54.4 ± 6.3 vs. 54.7 ± 6.2 , $p=0.8$) or race (Table 1). The prevalence of common comorbid conditions was comparable between groups. Sixty-one percent of the population had a history of hepatitis C infection, 71% had hypertension (Table 1). Between groups the use of antihypertensive medication that could affect heart rate results was similar (beta-blockers 10%; non-dihydropyridine calcium channel blockers 11%; $p>0.6$). There was a non-significant trend for the uninfected men to be more likely to be obese or overweight (Body Mass Index (BMI) > 25.0 kg/m²) than the HIV-infected men.

Overall, there was a strong correlation between the 6-MW and LDCW ($r=-0.85$, $p<.001$), with similar results in the HIV-infected and uninfected men. There was no difference in performance in the 6-MW

between HIV-infected and uninfected participants (Table 2). Using Enright's reference equation, the expected 6-MW (mean meters (\pm SD)) was 617 (\pm 48) and 598 (\pm 47) in HIV infected and uninfected groups, respectively. Time for the 400-meter LDCW in the HIV-infected subjects was a mean 18 seconds shorter than the uninfected subjects.

VO₂peak had a moderate and significant correlation with the 6-MW distance (meters) and 400-meter walk LDCW duration (minutes) in both subject groups (Figure 1). The 6-MW explained 25% and 32% of the variance in VO₂ peak in HIV-infected and uninfected subjects, respectively (Table 3). The 400-meter walk explained 27% and 23% of the variance in VO₂ peak in HIV-infected and uninfected subjects, respectively. Comparison between the HIV-infected and uninfected models showed no significant difference in Δ VO₂peak by unit change in ambulatory performance for either the 6-MW ($p=0.9$) or the LDCW ($p=0.8$) (Table 3). There was no significant difference in the corresponding values of the SEE across HIV groups ($p>0.1$). Results were unchanged in linear regression models adjusted for BMI (data not shown).

Discussion

This study presents novel results on ambulatory function in patients with and without HIV infection who have similar demographic and clinical characteristics. Among these men without history of CVD, ambulatory function was not significantly different by HIV status. The relationship between endurance walk tests and VO₂peak supports use of either the 6-MW or LDCW in HIV research to estimate aerobic exercise capacity. Endurance walk tests are valuable prognostic tools in HIV uninfected geriatric patient populations. Further investigation in larger and more diverse group of HIV-infected patients is needed to determine their clinical value.

This study offers the first direct comparison of endurance walk tests between HIV-infected and uninfected adults and includes validation with cardiorespiratory exercise testing. Despite the small and homogeneous study population, the findings have several important

Results	HIV-infected	HIV-uninfected	p-value*
6-MW (Mean (SE)):	N=45	N=37	
Distance, meters	545 (10)	531 (11)	0.3
Heart rate maximum, beats/min	113 (3)	115(3)	0.7
400-meter LDCW (Mean (SE)):	N=43	N=35	
Time, seconds	258.5 (4.9)	276.3 (5.5)	0.02
Heart rate maximum, beats/min	115 (3)	116 (3)	0.9

Six-minute walk (6-MW); long distance corridor walk (LDCW)

* Student's t-test

Table 2: Ambulatory function in HIV-infected and uninfected men.

implications. First, the results highlight the importance of a HIV uninfected comparison group when investigating non-HIV related outcomes. Several recent functional performance studies, showed reduced 6-MW distance [10,13,19] or LCDW time [14] in HIV-infected adults using normative data. In this study we found no significant difference in the 6-MW distance between HIV-infected on successful ART and uninfected men with similar age-related comorbidity, even with adjustment for BMI. This is not to say that AIDS does not adversely and significantly affect ambulatory function via mechanisms of muscle mass loss [25]. The prior reports of poor functional performance in HIV-infected adults with high CD4 cell count based on normative data is likely affected by differences in socioeconomic and clinical characteristics between the HIV-infected patients and the reference group. This possibility is supported by our finding that the estimated 6-MW distance in the HIV-infected adults was 12% lower than expected, based on a standard reference equation This mean difference of 73 meters represents both a statistical and clinical meaningful lower 6-MW distance. In contrast, the direct comparison of 6-MW distance between HIV groups found a mean difference of 14 meters, which is neither statistically or clinically significant.

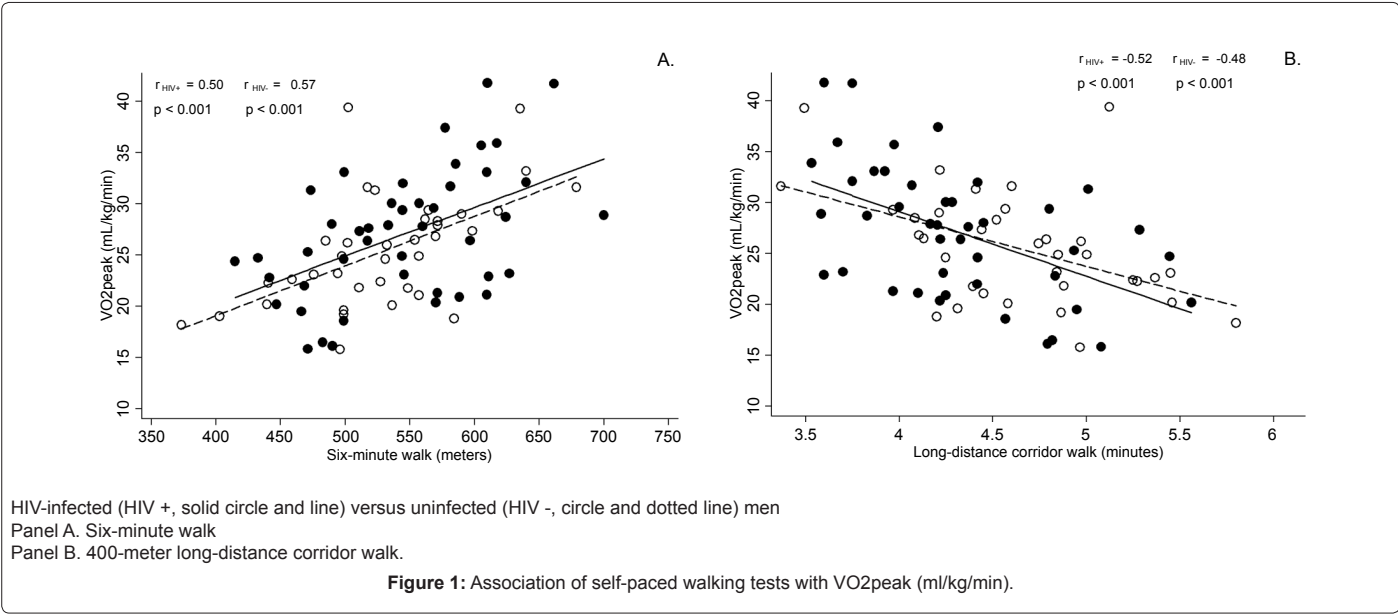
Our findings in this select group of men raise the question of the effect of age-related comorbidity on function in HIV-infected adults. Although we found no difference in ambulatory function between HIV groups, we excluded patients with known CVD and severe congestive heart failure as part of the CVD VACS study. Therefore our findings cannot be generalized to HIV-infected men at large; HIV-infected adults may still have a greater risk for poor ambulatory function due to increased disease burden of age-related conditions that are more common in HIV-infected adults. Further, disease severity may affect function. We previously reported that HIV-infected and uninfected patients in the Veterans Aging Cohort Study (VACS) had similar degree of limitations with physical activities [26]. However, when stratified by chronic lung disease, the HIV-infected patients had significantly lower reported physical function, with adjustment for demographics and smoking [27]. Future research with measures of ambulatory function in large diverse cohorts of HIV infected and uninfected older adults is needed to address these questions and provide insight into the clinical factors contributing to poor physical function in adults with chronic HIV infection.

To our knowledge, this is the first study to measure the LDCW in both HIV-infected and uninfected adults, and compare results with the 6-MW test. We found the time to complete the 400-meter walk was shorter in the HIV-infected men (4.31 minutes) compared to the uninfected men (4.63 minutes). Although this mean difference was statistically significant, it may not be clinically significant [28]. In healthy elderly men enrolled in the Baltimore Longitudinal Study of

Characteristics	HIV-infected N=45 n (%)	HIV-uninfected N=37 n (%)	p-value*
Age, years:			
<50	6 (13.3)	8 (21.6)	0.3
50-60	30 (66.7)	22 (59.5)	
>60	9 (20.0)	7 (18.9)	
Race, African American	45 (100)	36 (97.3)	0.2
Body Mass Index (BMI):			
<25 kg/m ²	23 (51.1)	12 (32.4)	0.09
\geq 25 kg/m ²	22 (48.9)	25 (67.6)	
Smoker, current	31 (69.0)	21 (56.8)	0.3
Comorbidity:			
Diabetes	12 (26.7)	7 (18.9)	0.4
Hepatitis C Infection	32 (71.1)	18 (55.6)	0.1
Hypertension	31 (68.9)	27 (73.0)	0.7
Chronic Pulmonary Disease	9 (20.0)	11 (29.7)	0.3
Dyslipidemia	16 (36.4)	8 (25.8)	0.3
Anemia, (Hgb<13 g/dl)	11(24.4)	14(37.8)	0.2

* chi-squared test

Table 1: Characteristics of HIV-infected and uninfected Men



Subjects	Six-minute walk, meters						400-meter LDCW, minutes				
	N	Model R ²	RMSE	Slope (ml/kg/min/m)		p*	N	Model R ²	RMSE	Slope (ml/kg/min/min)	
HIV-infected	45	0.25	5.51	β	SE		43	0.27	5.56	β	SE
Uninfected	37	0.32	4.56	0.047†	0.013	0.9	35	0.23	4.90	-6.35†	1.64
				0.048†	0.012					-4.87†	1.54

* difference in slope between models by the F-statistic
† p-value <0.01 for linear regression β coefficient
RMSE, root mean squared error

Table 3: Association of VO2peak (ml/kg/min) with performance in the six-minute walk and the 400-meter long-distance corridor walk (LDCW) by linear regression in HIV-infected and uninfected men.

Aging the mean time in the 400-meter walk is 4.07 minutes [24]. In community dwelling elderly adults each increased minute to perform the 400-meter walk is associated with a 29% increased mortality risk and 52% increased risk of mobility limitations [3]. Erlandson and colleagues recently performed the LDCW in a clinic-based cohort of 359 HIV-infected patients aged 45-65 years who received ART for at least 6 months and were 85% male [29]. Patients were not excluded based on comorbid conditions, with 18% (N 66) of the participants reporting recurrent falls in the prior year. Performance in the 400-meter walk among HIV-infected patients without fall history is comparable to our findings (4.38 minutes). However, the 400-meter time in those with recurrent falls is significantly slower (5.0 minutes), despite a comparable high mean CD4 cell count >500. Multiple comorbidities were predictive of falling history.

Performance in endurance walk tests is used as a surrogate for aerobic exercise capacity in patients at high risk for physical disability. Ross and colleagues conducted a meta-analysis which included over a thousand patients with diverse cardiorespiratory conditions from 11 different studies and found that the association between 6-MW and VO2peak was consistent and significant, regardless of differences in the 6-MW and exercise protocols [30]. Among all the studies, the average standard error of the estimate (3.82) was 27% of the mean VO2peak. Their results demonstrated that the greatest source of error was random within subject error, and not variability in testing methodology. Our results corroborate these findings for the first time in a study of HIV-infected patients that includes a control patient group from the same site and using same testing protocols. The average standard error of the

estimate (RMSE) of our 6-MW and VO2 models was not significantly different between HIV groups and represented 18-20% of the mean VO2peak.

In contrast, the LDCW is a relatively new functional performance measure with limited comparative studies. The LDCW and cardiorespiratory testing was performed in 102 healthy adults aged 60 to 91 years and showed a strong correlation between 400-meter time and VO2peak (-0.79) [24]. In a final model that also included stride length, ending systolic blood pressure, and a nonlinear correction factor, the 400-meter time explained 62.5% of the variance in VO2peak. However, findings were not compared to the 6-MW. We found the correlation of VO2peak with the 400-meter time or the 6-MW distance to be similar in magnitude, though appropriately inversely related as shorter time and longer distance both represent better ambulatory function. Further, the workload, based on maximum heart rate, was not significantly different between the walk tests in our study. Our findings support the use of either the 6-MW or the 400-meter LDCW as surrogate research outcomes for VO2peak in HIV-infected patients. However, we agree with current clinical practice; medical decisions regarding individual therapy, such as surgical risk, should be based on direct measure of cardiorespiratory fitness [31].

The generalizability of the study is limited by the narrow demographic characteristics of the HIV-infected veterans at the Baltimore VA Medical Center, who are primarily African American men. Further, as part of CVD VACS, this study also excluded patients with prevalent CVD (CAD, PVD, and stroke) at baseline with the intent of following them longitudinally. Therefore it is not surprising

that none of the participants had a 6-MW distance <350 meters, a prognostic threshold in patients with heart failure and lung disease. Only 2 participants required more than 5.5 minutes to complete the 400-meter course of the LDCW. However, the use of younger and healthier patients would only bias the associations to the null. While the prevalence of comorbid conditions that could affect self-paced walking and VO₂peak was similar between HIV-infected and uninfected men, disease duration and severity was not taken into consideration. The sample size limited our ability to test the association of comorbidity with function. Exercise physiologic research in a more diverse HIV patient population is warranted to investigate the mechanisms underlying loss of cardiorespiratory fitness and the impact on ambulatory function and mobility disability.

In conclusion, ambulatory function was not significantly associated with HIV infection in men with similar clinical characteristics, including absence of CVD history. The results from two different endurance walk tests provide the foundation for further research in a larger and more diverse patient population of HIV-infected adults to investigate age-related factors that predict mortality and mobility disability. Walking tests may provide a valuable outcome for interventional trials, especially in specific groups of HIV-infected patients, such as those with heart and lung disease.

Acknowledgements

This work was supported by the National Institutes of Health (K23AG024896, R01HL095136, U01AA13566, P60AG12583, P30AG028747, R01HL090342); and the Baltimore VA Geriatric Research, Clinical and Education Center. Author roles included study concept and design (LK,MF,KO), statistical analysis (JS, KO), data interpretation, manuscript preparation, editing, and writing (all authors). We appreciate the research coordinators for their dedication, the participants for their time and Xiao-Song Zhong for assistance with compiling data.

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