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Journal
AIDS, 28(18)

ISSN
0269-9370

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Publication Date
2014-11-28

DOI
10.1097/qad.0000000000000507

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2015 March 31.

Published in final edited form as:

AIDS. 2014 November 28; 28(18): 2711–2719. doi:10.1097/QAD.0000000000000507.

The relationship of physical performance with HIV disease and mortality

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Abstract

Objective—To evaluate whether HIV infection was associated with reduced physical performance, and to examine if reduced physical performance predicted mortality in our aging cohort of HIV-infected and HIV-uninfected persons.

Design—Prospective, observational cohort of current and former injection drug users in the AIDS Linked to the IntraVenous Experience study in Baltimore, Maryland, USA.

Methods—The Short Physical Performance Battery (SPPB) was used as an objective measure of physical performance and measured semiannually along with behavioral and demographic data. Correlates of reduced physical performance (SPPB score ≤10) were identified and the relationship between reduced physical performance, HIV infection and mortality was analyzed by Cox regression.

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Author contributions: M.G.: study conception and design, data analysis and interpretation, writing and revising article; K.C.: data interpretation, critical revision of article; J.A.: data analysis and interpretation, statistical expertise; D.A.P.: critical revision of article; T.B.: critical revision of the article; S.L.: critical revision of the article; N.G.: data analysis and interpretation, statistical expertise; S.H.M.: data acquisition, critical revision of article, J.G.: study conception and design, critical revision of article; K.V.P. study conception and design, critical revision of the article; G.D.K.: study conception and design, data acquisition, data analysis and interpretation, writing and revising the article. All authors approved the final version of this article.

Conflicts of interest

There are no conflicts of interest.

Results—Among 12 270 person-visits contributed by 1627 participants, the median age was 51, 30.3% were HIV-infected and 32.6% had an SPPB score 10 or less. In multivariable models, HIV infection was independently associated with 30% increased odds of reduced physical performance [odds ratio 1.30; 95% confidence interval (CI):1.12–1.52]. Reduced physical performance predicted mortality in a dose-response manner and within all HIV disease strata. Whereas reduced physical performance alone (hazard ratio 2.52, 95% CI: 1.59–4.00) and HIV infection alone (hazard ratio 2.78, 95% CI: 1.70–4.54) increased mortality, HIV-infected participants with reduced physical performance had a six-fold increased mortality risk (hazard ratio 6.03, 95% CI: 3.80–10.0) compared with HIV-uninfected participants with higher physical performance.

Conclusion—HIV infection was independently associated with reduced physical performance. HIV and reduced physical performance have independent and joint effects on mortality. Physical performance measurement may be an important research and clinical tool to predict adverse outcomes among aging HIV-infected persons.

Keywords

aging; HIV; injection drug use; mortality; physical function

Introduction

With effective antiretroviral therapy, HIV-infected adults are living longer and HIV has evolved into a chronic disease [1]. Studies suggest that HIV-infected persons may experience increased risk for age-related comorbidities such as cardiovascular, liver, bone or malignant disease [2–5], as well as multimorbidity [6], polypharmacy [7,8], and frailty [9–11]. These associations have been reported as the median age of the HIV-infected population in the United States now approaches 50 years. Although not considered ‘older’ compared with traditional geriatric populations, substantial concern exists among HIV-infected patients and their providers regarding best practices for supporting healthy aging [12].

For HIV-infected patients facing multimorbidity or other age-related concerns, functional status, a key component of geriatric assessments, may help to distinguish those persons at greatest risk for further age-related complications or decline. Functional status can be measured either subjectively through self-report or objectively through performance tests. The Short Physical Performance Battery (SPPB), an objective measure of lower extremity function, has been validated in the general population 65 years of age and older as a strong predictor of adverse outcomes such as disability, nursing home placement, and mortality [13,14]. The SPPB has been used extensively in research settings and can be integrated into clinical settings to identify patients at risk for adverse events [15,16]. Data on objective performance tests in HIV-infected populations have often been cross-sectional, without HIV-uninfected comparisons or linked to prospective assessment of associated clinical outcomes [17–19]. In the current study, we performed SPPB assessments in a large cohort of HIV-infected and epidemiologically similar HIV-uninfected persons over a 5-year-study period. We investigated how HIV infection and HIV-associated disease markers were associated with physical performance. Then, we examined the relationship of physical performance with mortality risk in this cohort.

Methods

Study participants

The AIDS Linked to the IntraVenous Experience (ALIVE) study is a prospective, observational cohort study that has followed community-recruited HIV-infected and at-risk injection drug users in Baltimore, Maryland, USA, since 1988. Persons 18 years or older reporting a history of injecting drugs were recruited in four waves from 1988 to 2008 [20]. Both HIV-infected and HIV-uninfected participants are followed in a shared research protocol with study visits every 6 months including standardized interviews, clinical examination, biospecimen collection and since July 2005, SPPB measurement. All participants provided written informed consent and the study was approved by the Johns Hopkins Institutional Review Board.

Data collection

Sociodemographic, behavioral, and clinical information was collected at each visit, generally measured as self-report of behavior in the prior 6 months. Hazardous alcohol use was measured using the Alcohol Use Disorders Identification Test (AUDIT) and depressive symptoms measured by the Center for Epidemiologic Studies Depression Scale (CES-D) scale. Comorbid conditions assessed included obesity (BMI $\geq$30 kg/m^2) and self-report of provider diagnosis of diabetes, hypertension, malignancy, cerebrovascular, cardiovascular, chronic lung, renal, or liver disease [9]. HIV-uninfected participants had HIV serology testing and HIV-infected participants had CD4$^+$ cell counts (measured by standard flow cytometry) and HIV-1 plasma RNA levels (limit of detection: 50 copies/ml; COBAS AmpliPrep/COBAS Taqman HIV-1 Monitor, Roche Diagnostics, Indianapolis, Indiana, USA) measured at each visit. Dates of death were obtained from review of death certificates and linkage with the National Death Index.

Short Physical Performance Battery

The SPPB was developed by the National Institute on Aging as an objective measure of lower extremity function and consists of three components: timed standing balance tests, timed walking test (gait speed), and timed chair rise [13]. For balance, participants were asked to stand and hold their feet in side by side, semi-tandem, and tandem positions for 10 s each. Gait speed was measured in two 4-m walks at a normal pace, with the faster of the two walks used in analysis. The timed chair-rising task was the time required to rise from a sitting to fully standing position five times as quickly as possible. Each component was scored as 0–4 points based on predetermined cut-offs to generate a total score from 0–12; higher scores correspond to better physical performance. The SPPB was administered by ALIVE research assistants trained initially by National Institute on Aging staff with periodic retraining.

Statistical analysis

We first examined the association of HIV status and HIV-related markers (current and nadir CD4$^+$ cell count; HIV viral suppression <50 copies/ml) with reduced physical performance defined as an SPPB score of 10 or less, a level which prior studies have associated with

increased risk for loss of mobility and disability; [13,21,22] sensitivity analyses with a less restrictive SPPB score cutpoint demonstrated qualitatively and quantitatively similar findings (data not shown). Multivariable logistic regression models calculated odds ratios (OR) with 95% confidence intervals (CI) while adjusting for confounders. Our unit of analysis was person-visits; generalized estimating equations accounted for within-person correlation of repeated measures across visits. We adjusted for sociodemographic, behavioral, and clinical factors significantly associated with physical performance with a *P* value <0.05 in multivariable models. As we previously identified a 'healthy drug user effect' within our cohort whereby higher functioning is required to support active drug use, and saw evidence of this in the analysis, drug-use variables were not incorporated into multivariable models [23]. Age was examined continuously (per 5-year increment), and race/ethnicity dichotomized as African American vs. other based on the predominance of African Americans in the cohort. Number of comorbid conditions was categorized as 0–1, 2, and at least 3. The effect of chronic liver disease, largely attributable to chronic hepatitis C virus infection in our population, was incorporated into models as a comorbid disease. Hazardous alcohol use was dichotomized at an AUDIT score of at least 8. Depressive symptoms were dichotomized at a CES-D score of at least 23 [9].

To evaluate the relationship between reduced physical performance and all-cause mortality, Kaplan–Meier survival analysis and Cox regression models were performed. The first person-visits occurred in 2005 and all-cause mortality data were available through 31 December 2010. Cox models estimated hazard ratios with 95% CI; inclusion of variables in the multivariable analyses was informed by prior mortality analyses in the cohort [9]. Models incorporated both time-fixed (sex, race) and time-updated (age, comorbidity, HIV status, and SPPB score) variables. Expected survival curves, based on the Cox model, were used to illustrate the relationship of SPPB scores with mortality adjusting for time-updated covariates taken at average values. To characterize whether the effect of physical performance on mortality differed by HIV status, stratified analyses were performed to evaluate the mortality risk associated with reduced physical performance in three groups: HIV-uninfected participants, HIV-infected participants with markers indicating poor control ($CD4^+$ cell count <200 cells/μl and HIV RNA >50 copies/ml; the subset previously identified as having the highest mortality), and all other HIV-infected participants with less-advanced HIV disease markers. The independent and joint effects of HIV status and reduced physical performance on mortality were examined using extended Kaplan–Meier curves and Cox models. Analyses were conducted in Stata version 12 (StataCorp LP, College Station, Texas, USA) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Physical performance of study participants

In total, 1627 participants contributed 12 270 person-visits from 2005 to 2010. Across all visits (Table 1), participants had a median age of 51 years, were predominantly African American, and approximately one-third female. HIV-infected participants accounted for 30.3% (*n* = 3715) of person-visits, had a median $CD4^+$ cell count of 339.5 cells/μl

[interquartile range (IQR), 191–513) and median viral load of 1.85 $\log_{10}$ copies/ml (IQR, 1.6–4.1).

SPPB scores of 10 or less, 11, and 12 occurred in 4001 (32.6%), 2899 (23.6%), and 5730 (43.8%) person-visits, respectively. Among the individual SPPB components, chair stands had the highest proportion of reduced performance with only 58.3% (n = 7154) having the maximum score of 4; 72.2% (n = 8864) and 85.3% (n = 10 463) of visits had the maximum score on the gait speed and balance tests, respectively.

Association of HIV with reduced physical performance

After accounting for age, female gender, educational attainment, depressive symptoms, and comorbidity associations with reduced physical performance (Supplemental Table, http://links.lww.com/QAD/A597), HIV infection was independently associated with a 30% increased odds of having an SPPB score 10 or less (OR 1.30, 95% CI: 1.12–1.52). In further multivariable analyses (Fig. 1), the odds of reduced physical performance status was moderated in HIV-infected participants with more favorable HIV markers (e.g. current or nadir $CD4^+$ cell count >200 cells/μl; viral suppression) but remained significantly increased compared with HIV-uninfected participants.

Association of reduced physical performance and HIV infection with mortality

During mortality follow-up through 2010, 165 (10%) deaths occurred with a mortality rate of 2.75 deaths per 100 person-years. As illustrated in adjusted survival curves in Fig. 2, participants with SPPB scores 10 or less had greater mortality during the subsequent 5 years compared with persons with higher physical performance (SPPB >10). In time-updated, multivariable Cox models adjusting for age, race/ethnicity, sex, comorbidities, and HIV infection, an SPPB score of 10 or less was associated with a 2.3-fold higher mortality compared with scores of more than 10 (hazard ratio 2.34, 95% CI: 1.67–3.27). While accounting for the significant effect of HIV infection on mortality, we observed a dose–response association of higher mortality with lower SPPB scores (Fig. 3) ranging from 2.26-fold higher mortality for SPPB scores of 11 to 4.25-fold higher mortality for scores less than 9. Importantly, the mortality risk associated with reduced physical performance was not limited to a subset of HIV-infected or HIV-uninfected persons as the risk estimates were qualitatively similar irrespective of HIV status or stage: the adjusted hazard ratios for SPPB 10 or less were 2.21 (95% CI: 1.37–3.55) in HIV-uninfected participants, 2.51 (95% CI: 1.33–4.76) for HIV-infected participants with poorly controlled HIV infection ($CD4^+$ cell counts <200 cells/μl and detectable HIV RNA), and 2.02 (95% CI: 0.95–4.3) for all other HIV-infected participants.

The independent and joint effects of HIV and reduced physical performance on mortality were next examined (illustrated in Supplemental Figure, http://links.lww.com/QAD/A597). Both HIV infection and reduced physical performance (SPPB ≤ 10) were independently associated with increased mortality but HIV-infected participants with reduced physical performance had the highest mortality risk. In multivariable Cox models incorporating HIV-uninfected participants with a SPPB score more than 10 as the referent group (Fig. 4), HIV-uninfected participants with reduced physical performance (SPPB ≤ 10) had a 2.5-fold

increased risk of death and HIV-infected participants with higher physical performance (SPPB > 10) had a 2.8-fold increased risk of death, whereas HIV-infected participants with reduced physical performance had a six-fold increased risk of death (hazard ratio 6.03, 95% CI: 3.80–10.0). In these models, the joint effect of HIV infection and reduced physical performance increased mortality risk in approximately a multiplicative manner.

Discussion

Within a cohort of middle-aged HIV-infected and HIV-uninfected persons with a median age of 51 years, we found that one-third of participants had evidence of impaired physical performance as measured by the SPPB. This finding alone is significant given that the SPPB is a test originally validated in HIV-uninfected adults aged 70 and older. After adjusting for sociodemographic factors and other comorbidities, HIV infection was associated with higher odds of reduced physical performance. Although poorly controlled HIV disease was associated with somewhat higher risk of reduced performance, even HIV-infected persons without advanced immunosuppression or with viral suppression had lower physical performance relative to epidemiologically comparable HIV-uninfected persons. Reduced physical performance categorized by SPPB scores was highly predictive of mortality, irrespective of HIV disease stage. Further, there was a multiplicative effect of HIV infection and reduced physical function on mortality risk. Our findings highlight the substantial impact of HIV disease on physical performance, support the growing recognition and importance of chronic HIV disease on age-related outcomes, and can inform strategies for the clinical management of aging HIV-infected persons.

To rigorously evaluate the relationship between physical performance and HIV infection, we employed a standardized, objective measure of physical performance, analyzed data from more than 1600 persons with more than 12 000 SPPB measurements, included a demographically and behaviorally similar HIV-uninfected comparison group, and adjusted for traditional factors associated with functional impairment. These robust data provide evidence for a deleterious effect of HIV on physical function. Prior studies of HIV and physical function as measured by the SPPB or its components have generally not included HIV-uninfected comparisons and often restricted their focus to only patients with well controlled HIV [17,18,24]. Recognizing that a clear majority of HIV-infected persons in the United States do not have well controlled HIV [25], we sought to examine how HIV severity contributed to function compared with an appropriate HIV-uninfected referent group. Our findings suggest that HIV disease severity may impact physical performance, with the greatest effect seen in patients with proximal $CD4^+$ cell counts below 200 cells/μl. Limited data from prior studies also indicated that advanced HIV disease may be associated with functional limitations assessed by both subjective and objective methods [19,26,27], although contrasting data have been reported [28]. These data suggest that improved HIV control and earlier initiation of anti-retroviral therapy could positively impact physical performance. However, our data also highlight that even persons with well controlled HIV disease may remain at higher risk than persons without HIV infection.

In the general population of older adults, the mechanisms underlying reduced physical performance are multifactorial. Similarly, in HIV-infected populations, physical

performance impairment likely results from multiple pathways, including both direct and indirect effects of HIV. In the elderly, chronic low-grade elevation of proinflammatory cytokines may contribute to loss of muscle mass, altered body composition, decreased physical function, frailty, and disability [29–32]. Similarly, HIV infection results in a proinflammatory state which can adversely impact physical function, especially with more advanced disease stage [33]. Higher levels of inflammatory markers have been associated with worse physical function in HIV-infected persons [24,34,35]. Other proposed mechanisms with supporting data include an HIV effect on muscle mass and body composition mediated through the growth hormone/insulin-like growth factor-1 axis [36], the hypothalamic-pituitary gonadal axis, or HIV effects on vitamin D levels [37], which have been implicated in lower extremity function [38].

SPPB scores are highly predictive of adverse outcomes such as disability, nursing home placement, hospital admission, and mortality in the general population of community-dwelling, HIV-uninfected older adults [13,21,39]. Similarly, we found that the SPPB score was able to predict mortality in our younger population in a dose–response fashion. Further, the risk estimate was similar irrespective of HIV disease stage, suggesting that the SPPB can predict outcomes in persons with well controlled HIV and those with more advanced HIV disease. We also observed a joint effect of HIV infection and reduced physical performance on mortality that appeared to increase the risk of death more than what would be expected from summing their independent effects. The key impact of this finding is the increased potential for identification of persons most at risk for adverse clinical outcomes. Such identification can facilitate interventions such as physical therapy or exercise to improve muscle strength and lower extremity function to ameliorate risk.

The best approach for assessing physical function among HIV-infected populations remains unknown. Additionally, confusion often surrounds the distinction between physical function and other age-associated conditions such as frailty. Previously, we have shown frailty to be associated with both HIV infection and mortality [9] However, frailty and physical function represent related but separate entities [40]; only 21% of participant visits with reduced physical performance included in this analysis also met criteria for frailty. Notably, the SPPB may detect earlier deficits more amenable to intervention than the frailty phenotype.

The SPPB is easy to administer and standardized training videos are readily available. Given concerns for ceiling effects in younger populations, the SPPB can be modified to increase the difficulty of the test, such as by increasing the number of chair stands, increasing the time to hold balance positions, or by adding a one-leg stand balance test. Other objective measures of physical function (e.g. gait speed alone, grip strength), and self-reported function (e.g. activities of daily living or instrumental activities of daily living) have been proposed as tools to identify aging HIV-infected persons at high-risk for functional limitations or death. To date, the relative performance of these measures for predicting mortality or other adverse outcomes in HIV-infected persons has not been well characterized. Consensus regarding standardized approaches for measurement of physical function would be of clinical benefit and would facilitate comparisons across cohorts and support expanded research on complications and management of persons aging with HIV infection.

Our study results may not be generalizable to all HIV-infected populations because this is a primarily African American, urban cohort of injection drug users. However, this limitation also reflects a strength as our study population represents disadvantaged African Americans with the highest morbidity and mortality burden from HIV and chronic diseases, and with the greatest disparities in care. There remains substantial need for focused research and intervention in this population.

In summary, we provide evidence that HIV disease is strongly associated with reduced physical performance and that HIV infection and reduced physical performance may act in concert to increase mortality. Our findings highlight the need to integrate geriatric principles such as functional assessment into the care of older HIV-infected adults and also can inform the design of clinical interventions to improve outcomes in this population. The SPPB may be an effective tool for use in both clinical and research settings to support the healthy aging of persons with HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge the continued efforts of both ALIVE study participants and the ALIVE clinic and data staff.

This work was supported by the National Institutes of Health (grants U01-DA-036297, R01-DA-0433, R01-DA-12568, RC1-AI-086053, and 5-T32-AG000212 [MG]). T.B. is a consultant for EMD-Serono, ViiV Healthcare, Gilead, Merck, and Abbvie. M.G. received one-time honoraria for reviewing IAS-USA cases on the web.

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	No. (%) with SPPB ≤10 4001 (32.6% of all study visits)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
HIV-uninfected	2701 (31.6)	Ref	Ref
HIV-infected	1300 (35.0)	1.30 (1.12–1.51)	1.30 (1.12–1.52)
CD4 nadir < 200 cells/μl	830 (35.9)	1.38 (1.17–1.65)	1.36 (1.14–1.62)
CD4 nadir ≥ 200 cells/μl	457 (33.4)	1.18 (0.98–1.44)	1.22 (1.00–1.50)
CD4 count < 200 cells/μl	343 (36.0)	1.44 (1.19–1.75)	1.46 (1.20–1.79)
CD4 count ≥ 200 cells/μl	944 (34.7)	1.25 (1.07–1.47)	1.25 (1.06–1.47)
Detectable viral load	654 (34.4)	1.31 (1.11–1.55)	1.36 (1.14–1.60)
Undetactable viral load	636 (35.7)	1.30 (1.09–1.54)	1.26 (1.06–1.50)

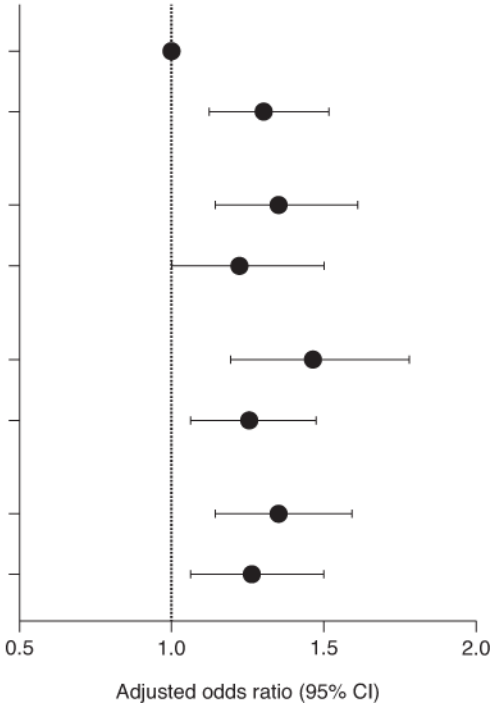

Fig. 1. Association of HIV infection and HIV-related disease markers with reduced physical performance (Short Physical Performance Battery score ≤ 10) among AIDS Linked to the Intra-Venous Experience participants across all visits (*n* = 12 270)

The vertical dotted line at 1.0 represents the referent group of HIV-uninfected participants. Each group of risk estimates represents a separate multivariable model including adjustment for age, sex, race/ethnicity, educational attainment, depressive symptoms, and number of comorbidities.

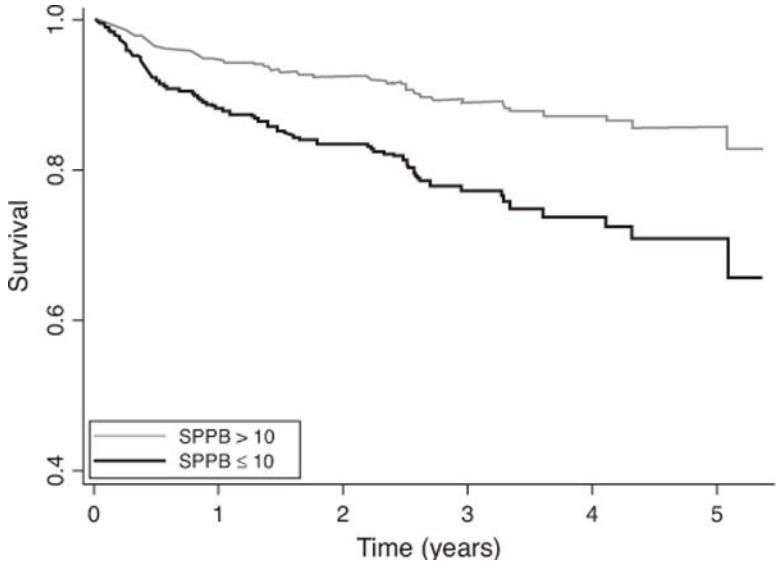

Fig. 2.

Survival differences associated with reduced physical performance [Short Physical Performance Battery (SPPB) score ≤ 10] compared with participants with higher physical performance (SPPB score >10).

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
SPPB 12	Ref	Ref
SPPB 11	2.26 (1.39–3.68)	2.26 (1.37–3.72)
SPPB 10	3.47 (2.09–5.76)	2.89 (1.70–4.92)
SPPB 9	4.18 (2.36–7.40)	3.39 (1.86–6.18)
SPPB < 9	5.49 (3.46–8.71)	4.25 (2.58–7.01)
HIV-uninfected	Ref	Ref
HIV-infected	2.56 (1.89–3.50)	2.57 (1.87–3.53)

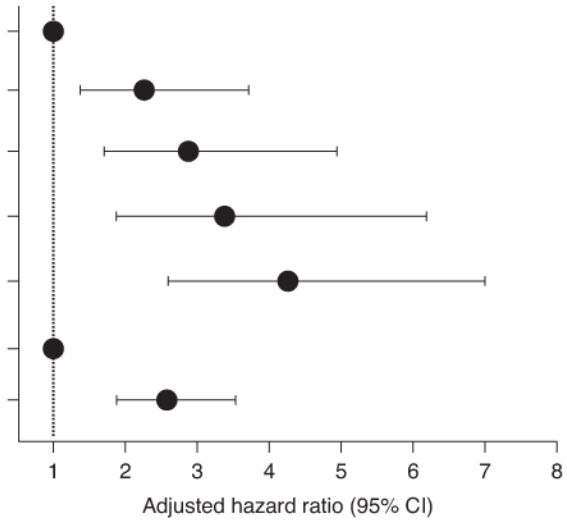

Fig. 3. Association of Short Physical Performance Battery score with all-cause mortality among ALIVE participants

ALIVE, AIDS Linked to the IntraVenous Experience; SPPB, Short Physical Performance Battery. [a]Hazard ratios were estimated from a single multivariable model including adjustment for age, sex, race/ethnicity, and number of comorbidites in addition to SPPB score categories and HIV status. The vertical dotted line at 1.0 represents the referent groups for physical performance category (SPPB score = 12) and for HIV status (HIV-uninfected participants).

	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
HIV-uninfected and SPPB > 10	Ref	Ref
HIV-uninfected and SPPB ≤ 10	3.39 (2.18–5.27)	2.52 (1.59–4.00)
HIV-infected and SPPB > 10	2.93 (1.81–4.74)	2.78 (1.70–4.54)
HIV-infected and SPPB ≤ 10	7.35 (4.69–11.5)	6.03 (3.80–10.0)

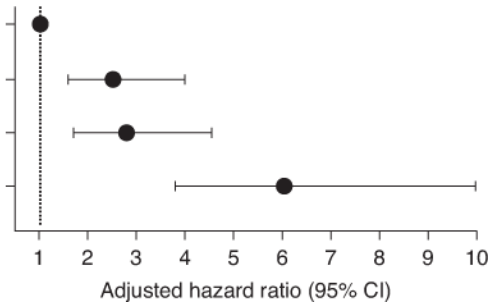

Fig. 4. Independent and joint effects of reduced physical performance and HIV infection on mortality

SPPB, Short Physical Performance Battery. [a]Hazard ratios were estimated for reduced physical performance only, for HIV infection only, and for both HIV infection and reduced physical performance compared with HIV-uninfected persons with higher physical performance as the referent group in a single multivariable model including adjustment for age, sex, race/ethnicity, and number of comorbidites in addition to the SPPB score/HIV status categorical variable. The vertical dotted line at 1.0 represents the single referent group of HIV-uninfected participants with higher physical performance (SPPB score >10).

Table 1

Characteristics of ALIVE participants (*N* = 1627) by HIV status at baseline and across all study visits (*N* = 12 270).

Characteristic	HIV-infected participants		HIV-uninfected participants	
	Baseline *N* = 532 *N* (%) or median (IQR)	**All visits *N* = 3715 *N* (%) or median (IQR)**	**Baseline *N* = 1095 *N* (%) or median (IQR)**	**All visits *N*=8555 *N* (%) or median (IQR)**
Age	48.0 (44.0–52.3)	50.6 (45.9–54.9)	47.5 (41.5–52.4)	50.9 (45.5–55.9)
Women	191 (35.9)	1294 (34.8)	370 (33.8)	2887 (33.8)
African American	490 (92.1)	3496 (94.1)	912 (83.3)	7589 (88.7)
At least high school education	195 (37.0)	1332 (36.2)	489 (44.7)	3751 (43.9)
Not married/common law	495 (93.8)	3477 (94.4)	1002 (91.6)	7828 (91.6)
Currently employed[a]	84 (15.9)	508 (13.7)	293 (26.9)	2011 (23.5)
Income <$5000[a]	414 (80.4)	2625 (72.8)	827 (78.7)	6253 (74.9)
Homeless[a]	77 (14.5)	294 (8.0)	192 (17.6)	811 (9.5)
Incarcerated[a,b]	62 (11.7)	251 (6.8)	141 (12.9)	646 (7.6)
Comorbid conditions[a,c]				
0–1 comorbid conditions	363 (70.6)	2377 (66.4)	762 (75.2)	5443 (66.2)
2 comorbid conditions	98 (19.1)	750 (21.0)	156 (15.4)	1539 (18.7)
≥3 comorbid conditions	53 (10.3)	451 (12.6)	95 (9.4)	1237 (15.1)
HCV-infected[d]	327 (78.8)	2602 (79.3)	612 (62.8)	5155 (64.7)
Depressive symptoms[e]	126 (23.8)	781 (21.1)	262 (24.0)	1841 (21.5)
Current smoker[a]	424 (80.2)	2881 (77.8)	930 (85.2)	6878 (80.5)
Hazardous alcohol use[a,f]	92 (17.4)	624 (16.8)	260 (23.8)	1833 (21.5)
Injection drug use[a]	199 (37.5)	999 (26.9)	520 (47.6)	2779 (32.5)
Noninjection drug use[a]	199 (37.7)	1159 (31.3)	541 (49.6)	3300 (38.6)
$CD4^+$ cell count (cells/mm^3)	331.5 (182–499)	339.5 (191–513)	–	–
$CD4^+$ nadir (cells/μl)	182 (70–296)	152.5 (54–251)	–	–
Viral load (log 10 copies/ml)	2.5 (1.6–4.3)	1.85 (1.6–4.1)	–	–
On HAART[a]	286 (56.2)	2411 (65.6)	–	–

ALIVE, AIDS Linked to the IntraVenous Experience; IQR, interquartile range.

[a] Within the past 6 months.

[b] Defined as period of at least 1 week.

[c] Comorbidities include obesity (BMI ≥30 kg/m^2), diabetes, hypertension, malignancy, cerebrovascular, cardiovascular, renal, chronic lung, or liver disease.

[d] HCV-infected defined as HCV antibody positive with detectable HCV RNA.

[e] Depressive symptoms defined as CES-D ≥23.

[f] Defined as AUDIT score ≥8.