The Journal of Infectious Diseases

BRIEF REPORT

Association Between Frailty and Components of the Frailty Phenotype With Modifiable Risk Factors and Antiretroviral Therapy

Kristine M. Erlandson,[1] Kunling Wu,[2] Susan L Koletar,[4] Robert C. Kalayjian,[5] Ronald J. Ellis,[6] Babafemi Taiwo,[7] Frank J Palella Jr,[7] and Katherine Tassiopoulos[3]

[1]Department of Medicine, University of Colorado–Anschutz Medical Campus, Aurora, [2]Center for Biostatistics in Aids Research and [3]Department of Epidemiology, Harvard T. H. Chan, School of Public Health, Boston, Massachusetts, [4]Department of Internal Medicine, Ohio State University, Columbus, [5]Department of Medicine, MetroHealth Medical Center, Cleveland, Ohio, [6]Department of Neurosciences, University of California–San Diego, and[7]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

The impact of antiretroviral therapy (ART) on frailty among human immunodeficiency virus (HIV)–infected adults has not been well described. HIV-infected participants aged ≥40 years with initial ART receipt through a randomized, controlled AIDS Clinical Trials Group trial completed a frailty assessment. Ordinal logistic regression models examined factors associated with frailty. Of 1016 participants, 6% were frail, and 38% were prefrail. Frailty was associated with lower education, older age, Medicare/Medicaid, initial efavirenz, smoking, obesity, and neurocognitive impairment; physical activity and alcohol use were protective. The associations with ART require further investigation, and associations between frailty and modifiable factors provide targets for future interventions.

Keywords. HIV; frail elderly; muscle strength; mobility limitation; antiretroviral therapy.

With combination antiretroviral therapy (ART), longer life expectancy is changing the demographics of the human immunodeficiency virus (HIV) epidemic, and an estimated 70% of the HIV-infected population will be aged >50 by 2030 [1]. Even with effective ART, frailty and physical function impairments are common and have been associated with increased risk of falls, hospitalizations, and mortality [2–6]. In addition to the composite frailty phenotype, measurement of the single, objective component of gait speed may be equally predictive of morbidity and mortality and may be easier to implement in the clinical or research setting [7]. Careful investigation of factors contributing to frailty and gait speed can guide the use of these tests in the clinical or research setting.

The impact of specific initial or ongoing ART drugs on the development of frailty has been difficult to evaluate. Although prior studies have suggested that protease inhibitors might be associated with an increased risk of frailty [8], these results may have been influenced by multiple factors that affect ART selection.

The goal of this study was to describe the impact of initial and ongoing ART selection in addition to other participant characteristics on frailty in HIV-infected adults currently enrolled in the AIDS Clinical Trials Group (ACTG) Study A5322, the HIV Infection, Aging, and Immune Function Long-Term Observational Study (HAILO).

METHODS

Participants were enrolled in HAILO, an ongoing observational cohort study of HIV-infected adults who initiated ART through an ACTG randomized clinical trial and were previously followed in the ACTG A5001 study [9]. All A5001 participants aged ≥40 years were eligible. Enrollment occurred during 2014–2015 with subsequent semiannual follow-up visits. All participants signed a written informed consent before enrollment, and the study was approved by the local institutional review board at each site.

Frailty Assessment

Frailty was assessed at study entry using the criteria established by Fried et al [10]. Weakness was assessed by the average of 3 dominant hand grip strength measurements and defined by applying previously defined sex and body mass index (BMI) cutoffs [10]. Slowness was defined by the average of 2 readings on a 4-meter walk: men ≤173 cm and women ≤159 cm in height who required ≥6.22 seconds or men >173 cm and women >159 cm who required ≥5.33 seconds to complete the walk met the criterion for slowness [10]; gait speed was also dichotomized at ≤1 or >1 m/sec [7]. Weight loss was defined by self-report of an unintentional weight loss of ≥10 pounds during the past year. Low activity was defined as being "limited a lot" in response to the Short Form (SF)–36 question, "Does your health limit you in vigorous activities such as running, lifting heavy objects, or participating in strenuous sports?" Exhaustion was defined as experiencing at least 3–4 times per week the feeling that "everything I do is an effort" or "sometimes I just cannot get going." Participants were considered nonfrail if they met 0 components, prefrail if they met 1 or 2 components, and frail if they met 3–5 components. Gait speed was also evaluated individually [7].

Received 8 November 2016; editorial decision 23 January 2017; accepted 24 January 2017; published online February 07, 2017.

Presented in part: Conference on Retroviruses and Opportunistic Infection, Boston, Massachusetts, February 2016. Abstract 719.

Correspondence: K. M. Erlandson, MD, 12700 E 19th Ave, Mail Stop B168, Aurora, CO 80045 (kristine.erlandson@ucdenver.edu).

The Journal of Infectious Diseases® 2017;215:933–7

DOI: 10.1093/infdis/jix063

Covariates

Antiretroviral therapy exposure was examined as the initial randomized regimen and the regimen at HAILO enrollment (baseline) and was categorized as a dual-drug nucleoside/nucleotide reverse-transcriptase inhibitor backbone, with either a protease inhibitor (PI), no-nucleoside reverse transcriptase inhibitor (NNRTI), or integrase strand transfer inhibitor (INSTI), or as other therapy. Any prior exposure to and duration of zidovudine (ZDV), stavudine (D4T), or didanosine (DDI); years of cumulative NNRTI; PI, or INSTI use; and years since ART initiation were also considered.

Physical activity was self-reported using the International Physical Activity Questionnaire [11]; outcomes were dichotomized as low (≤2) or moderate/high (≥3) days per week of moderate or vigorous intensity physical activity. Neurologic impairment was assessed with the A5001 Neuroscreen [12], using normalized, demographic-adjusted scores of the Trails-Making A, Trails-Making B, and Digit Symbol tests. Impairment was considered if a participant had at least 1 test score that was 2 standard deviations (SD) below the mean or scores that were at least 1 SD below the mean on 2 separate tests. Additional covariates are described in the Table 2 note.

Statistical Methods

The outcomes were defined as (1) frailty as a 3 category variable—frail, prefrail, and nonfrail and (2) slow gait speed (>4 seconds in a 4-meter walk). We described the prevalence of the prespecified categories for each outcome. Characteristics were compared between frail, prefrail, and nonfrail individuals using chi-square or Fisher's exact tests for categorical variables and *t* tests or Kruskal–Wallis tests for continuous variables. Ordinal logistic regression models identified factors associated with an increase in frailty from nonfrail to prefrail or from prefrail to frail, and logistic regression models were used to identify factors associated with slow gait. The score test was used to check the assumption of proportional odds for the ordinal logistic models. Covariates were evaluated separately in each model for each outcome, and those with $P < .10$ in univariable models were retained in the final, multivariable models. For highly correlated variables, those with the largest effect estimate were retained in the final models. No adjustments for multiple comparisons were made.

Secondary analyses were conducted to further investigate the potential role of initial ART regimen. Models were built that included initial ART regimen types and that adjusted only for factors assessed before or at the same time as ART initiation. To explore a cohort effect, a sensitivity analysis was performed of HAILO participants who had received their initial ART through A5202, an ART initiation study that randomized participants to efavirenz (EFV) versus boosted atazanavir (ATV/r) with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC).

RESULTS

Frailty

Among 1016 participants with frailty data at baseline, 62 (6%) were frail, 390 (38%) were prefrail, and 564 (56%) were nonfrail. Baseline characteristics of the study population by frailty group are shown in Table 1. Briefly, females, nonwhites, and persons with Medicare/Medicaid health insurance were more likely to be prefrail or frail. Significant differences in age and CD4 count were seen across frailty groups; years since ART initiation, nadir

Table 1. Participant Characteristics at Baseline (Enrollment Into HAILO, A5322), Overall and by Frailty Group

			Frailty status at baseline			
Characteristic		Total (n = 1016)	Not frail (n = 564)	Prefrail (n = 390)	Frail (n = 62)	*P* value
Sex	Female	195 (19%)	83 (15%)	95 (24%)	17 (27%)	<.001
Race/ethnicity	White non-Hispanic	485 (48%)	305 (54%)	156 (40%)	24 (39%)	<.001
	Black non-Hispanic	301 (30%)	146 (26%)	131 (34%)	24 (39%)	
	Hispanic (regardless of race)	200 (20%)	93 (16%)	94 (24%)	13 (21%)	
	Other[a]	28 (3%)	18 (3%)	9 (2%)	1 (2%)	
Age, y	<50	446 (44%)	283 (50%)	151 (39%)	12 (19%)	<.001
	50–59	412 (41%)	204 (36%)	171 (44%)	37 (60%)	
	≥60	158 (16%)	77 (14%)	68 (17%)	13 (21%)	
Health insurance	No medical coverage	196 (19%)	100 (18%)	90 (23%)	6 (10%)	<.001
	Medicare/Medicaid	323 (32%)	132 (23%)	149 (38%)	42 (68%)	
	Private	422 (42%)	291 (52%)	120 (31%)	11 (18%)	
	Other	63 (6%)	34 (6%)	26 (7%)	3 (5%)	
CD4 count, cells/mm^3	<350	126 (12%)	56 (10%)	59 (15%)	11 (18%)	.01
	350–500	204 (20%)	120 (21%)	79 (20%)	5 (8%)	
	>500	680 (67%)	385 (68%)	249 (64%)	46 (74%)	

Other baseline variables that were not significantly different by frailty status included nadir CD4 ($P = .95$), HIV-1 RNA at baseline <200 ($P = .30$), years since antiretroviral (ART) initiation ($P = .17$), initial randomized ART ($P = .37$), didanosine/stavudine use on or before baseline ($P = .29$), zidovudine use on or before baseline ($P = .35$), or ART regimen at baseline ($P = .99$).

[a]Other included Asian, Pacific Islander, American Indian, Alaskan Native, or >1 race.

Table 2. Unadjusted and Adjusted Associations Between Demographics, Human Immunodeficiency Virus, Comorbidities and Frailty Status

		Univariable[a] (n = 1016)		Multivariable[a] (n = 867)	
Variables		Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Sex	Female	1.87 (1.38–2.53)	<.001	1.23 (0.83–1.81)	.30
Race, vs white, non-Hispanic	Black, non-Hispanic	1.79 (1.35–2.38)	<.001	1.15 (0.81–1.64)	.43
	Hispanic + other	1.69 (1.24–2.31)	<.001	1.34 (0.86–2.08)	.19
Baseline age, vs 40–49	50–59	1.87 (1.43–2.45)	<.001	**1.78 (1.29–2.44)**	**<.001**
	≥60	1.89 (1.32–2.71)	<.001	1.48 (0.94–2.32)	.09
Education, vs >high school	≤High school	2.35 (1.82–3.02)	<.001	**1.57 (1.13–2.17)**	**.007**
Health insurance, vs Medicare/Medicaid	No coverage	0.58 (0.41–0.82)	.002	**0.67 (0.44–1.04)**	**.07**
	Private or other	0.31 (0.24–0.42)	<.001	**0.58 (0.41–0.82)**	**.002**
Baseline CD4 cell count, vs >500	<350	1.59 (1.10–2.3)	.01	1.52 (0.84–2.74)	.16
	350–500	0.86 (0.63–1.17)	.34	0.98 (0.67–1.43)	>.90
Pre-ART HIV RNA copies/mL, vs ≤100 000	≥100 000	0.78 (0.61–1.01)	.06	**0.73 (0.53–1.00)**	**.05**
Initial ART regimen, vs NRTI-backbone + PI	NRTI-backbone + NNRTI	1.35 (1.00–1.83)	.05	**1.47 (1.02–2.11)**	**.04**
	NRTI-backbone + INSTI	1.26 (0.83–1.90)	.28	1.02 (0.62–1.7)	>.90
	Other	1.14 (0.82–1.58)	.43	1.16 (0.78–1.71)	.46
Hepatitis C serology, vs never positive[b]	Ever positive	1.74 (1.21–2.51)	.003	**1.55 (1.01–2.38)**	**.05**
History of smoking, current + prior	Never	1.44 (1.12–1.84)	.004	**1.37 (1.01–1.86)**	**.04**
Current alcohol use at baseline, vs none[c]	Light	0.50 (0.38–0.67)	<.001	0.62 (0.44– 0.86)	**.004**
	Moderate/heavy	0.44 (0.31–0.61)	<.001	0.52 (0.35– 0.77)	**.001**
Days of vigorous/moderate activities/ week, vs ≥3	<3	2.10 (1.63–2.70)	<.001	**1.95 (1.46–2.61)**	**<.001**
Obesity at baseline[d]		1.54 (1.18–2.01)	.001	**1.42 (1.02–1.98)**	**.04**
Obesity at ART initiation[d]		1.60 (1.16–2.20)	.004		
Weight change within the first year of ART, kg	Every 1-kg increase	1.02 (1.00–1.04)	.02	1.01 (0.99–1.03)	.35
Cardiovascular disease		2.26 (1.38–3.72)	.001	1.52 (0.86–2.70)	.15
Renal disease[e]		2.35 (1.58–3.48)	<.001	1.52 (0.97–2.40)	.07
Cancer within past 5 years[f]		2.01 (1.03–3.91)	.04	1.22 (0.53–2.81)	.65
Diabetes[g]		2.24 (1.59–3.15)	<.001	1.21 (0.79–1.85)	.39
Hypertension[h]		1.47 (1.10–1.95)	.009	1.26 (0.87–1.82)	.22
Neuro-impairment at baseline		2.52 (1.80–3.52)	<.001	**2.04 (1.37–3.03)**	**<.001**

Bold indicates *P* value ≤0.05. Other covariates considered but not associated ($P \geq .10$) with frailty in univariable models included: nadir CD4 count, baseline antiretroviral therapy (ART) regimen, years since ART initiation, any zidovudine use, any didanosine or stavudine use, cumulative integrase strand transfer inhibitor, protease inhibitor and nonnucleoside reverse transcriptase inhibitor use, substance use, weight change between A5001 entry and baseline, baseline low-density lipoprotein cholesterol, liver disease, and depression. Substance use included history of use of illicit substances, including tobacco. Liver disease was defined as cirrhosis, ascites, esophageal/gastric varices, or hepatic encephalopathy during A5001/parent studies, or as cirrhosis or hepatic steatosis on HAILO.

Depression was defined as current use of an antidepressant medication, an ongoing diagnosis of major depression, or grade 3 or greater major depression symptoms.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Outcome modeled is an increase in 1 frailty level (from nonfrail to prefrail or prefrail to frail).

[b]Hepatitis C virus infection was defined as any positive hepatitis C antibody.

[c]Alcohol use in the past 30 days was categorized as abstainer, light (men <7 drinks/week, women <3 drinks/week; no binge drinking), moderate (men 7–14 drinks/week, women 3–7 drinks/week; no binge drinking), or heavy use (men >14 drinks/week, women >7 drinks/week, and/or binge drinking). Binge drinking, ≥5 drinks for men and ≥4 drinks for women within a 2-hour period, was separately considered as abstainer, no binging, binging once/month, or binging more than once/month.

[d]BMI was categorized as underweight (body mass index [BMI] < 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–30 kg/m^2), and obese (>30 kg/m^2).

[e]Renal disease was defined as estimated glomerular filtration rate (eGFR) measurements <60 mL/min/1.73 m^2 measured at least 3 months apart with no intervening eGFR ≥60 based on the CKD-EPI equation.

[f]Cancer was defined as any malignancy within 5 years except nonmelanoma skin cancer.

[g]Diabetes was defined as 2 consecutive nonfasting serum glucose measurements >200 mg/dL, 2 fasting glucoses ≥126 mg/dL within 1 year, a diagnosis of diabetes, or a hemoglobin A1C ≥6.5%.

[h]Hypertension was defined as use of antihypertensive medications, a diagnosis of hypertension, or a systolic blood pressure of ≥140 mm Hg or diastolic of ≥90 mm Hg at 2 consecutive visits.

CD4, and baseline HIV-1 RNA at baseline were similar across groups.

Associations between greater frailty and demographic factors, comorbidities, HIV disease/treatment, and lifestyle characteristics are summarized in Table 2. In multivariable models, the odds of an increase in frailty level were significantly higher among participants aged 50–59 years (vs younger), active or prior smokers, persons with less education, lower physical activity, hepatitis C virus infection, neurocognitive impairment, and obesity, and persons who received NNRTI-based

initial randomized ART therapy (vs PI; 100% EFV), but not NNRTI duration or use at time of frailty assessment. The odds of increased frailty were significantly lower among participants with private insurance compared with Medicare or Medicaid-based plans, higher pre-ART HIV-1 RNA levels, and any alcohol use. In a separate model that adjusted only for pretreatment initiation factors, the effect upon frailty of having received initial ART with an NNRTI (EFV) was unchanged (adjusted odds ratio [OR] = 1.57; 95% confidence interval [CI] = 1.15–2.16]) (not shown). In a sensitivity analysis restricted to HAILO participants from A5202, an ART initiation study that randomized participants to EFV vs ATV/r with TDF/FTC or ABC/3TC (n = 228), similar effects were seen with age, socioeconomic variables, pre-ART HIV-1 RNA level, physical activity, and neurocognitive impairment (not shown). Efavirenz was not associated with a greater odds of frailty compared with ATV/r (univariable OR = 1.01; 95% CI = .62–1.64; $P > .90$), but a trend was seen for a protective effect with TDF/FTC versus ABC/3TC (multivariable OR = 0.58; 95% CI = .32–1.05; $P = .07$).

Gait Speed

The median 4-meter walk time was 3.9 (interquartile range = 3.3–4.4) seconds. One hundred thirty-nine participants (14%) had a gait speed slower than 0.8 m/sec and 414 (41%) had a gait speed equal to or slower than 1.0 m/sec. Participant characteristics by gait speed are shown in Supplementary Table 1. The odds of slower gait speed (≤ 1 m/sec) were significantly higher among participants who were black or Hispanic, had less education, had lower physical activity, had Medicare/Medicaid versus private insurance coverage, had previously received either DDI or D4T at any time point, had gained more weight during the first year following ART initiation, or had renal disease or neurocognitive impairment; baseline use of an INSTI-based regimen and light alcohol use were protective.

DISCUSSION

In a large cohort of well-characterized, HIV-infected, middle-aged and older adults who initiated ART through an ACTG randomized clinical trial, we found a significant association between frailty and initial assignment of NNRTI-based (all EFV) therapy compared with PI-based therapy, and a protective effect of baseline INSTI use compared with PI use on gait speed.

Although the association between initial EFV use and frailty is intriguing, several points should be considered when interpreting these findings: (1) we found no association with frailty for the duration of EFV or use of EFV at the time of the frailty assessment; (2) we found no association with frailty in a sensitivity analysis of participants randomized to only EFV- or PI-based ART, although the sample size was smaller; and 3) the time from initial NNRTI exposure to the frailty assessment was variable and spanned many years in most participants. Thus, we do not know whether merely exposure to an NNRTI-based therapy (primarily EFV) is associated with subsequent frailty or whether the association is simply a marker for a subset of participants with poor EFV tolerability (hence the lack of association with NNRTI duration), unmeasured confounders at the time of ART initiation such as time elapsed from HIV diagnosis, or loss to follow-up. In contrast, INSTI use at baseline, but not prior use or INSTI duration, was associated with a protective effect on gait speed. Baseline INSTI use included both participants initially randomized to and participants who switched to an INSTI drug. For both drug associations, the findings remained significant in multivariable models adjusted for many factors impacting baseline ART use.

The multifactorial nature of frailty is noted by the variety of covariates that were predictive of increasing frailty, including demographic, socioeconomic, and lifestyle factors and comorbidities. Socioeconomic inequalities and disparities throughout a lifetime are important determinants of health, such that experiences in childhood and young adulthood, in addition to midlife and older age, all appear to contribute to frailty in older age [13]. Socioeconomic factors may, in part, be mediated by other behavioral changes such as differences in diet, leisure-time activities [14], or factors associated with chronic stress. Not surprisingly, we found that neurocognitive impairment was one of the strongest risk factors for frailty and slow gait. In contrast, no other comorbidities were associated with both outcomes.

Limitations should be acknowledged. The participants have been continuously enrolled in ART treatment trials and observational studies for a median of 7.8 years and may not be fully representative of the overall HIV epidemic. This cross-sectional analysis precludes us from determining the temporal relationship between covariates and frailty. Frailty assessments were only available beginning at the time of HAILO enrollment, and the effect of ART on frailty, gait, and grip characteristics at the time of therapy initiation cannot be determined. Minor differences in 4-meter walk and grip strength measurement techniques across sites were likely present, although training and quality control procedures were implemented to limit variation within and between sites. Lastly, we acknowledge that self-report of physical activity is a poor measure of actual activity and hepatitis C antibody does not reflect active infection.

In summary, among older HIV-infected adults, we observed an association between frailty and NNRTI-based initial ART and a protective effect of INSTI therapy on gait speed. Both findings require further investigation but suggest that INSTI-based regimens may be preferred for older, HIV-infected adults at risk for frailty or mobility impairment. The higher burden of frailty among HIV-infected adults with socioeconomic disadvantages or neurocognitive impairment identifies individuals with high risk for hospitalizations, mobility decline, and mortality. This population should constitute a priority target for frailty identification and close clinical follow-up. Lastly, modifiable factors

(smoking, low physical activity, obesity) were strongly associated with increased frailty and provide ideal targets for future interventions to prevent or slow the frailty trajectory.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgements. K. M. E., K. W., and K. T. developed the analysis and interpretation. K. W. performed the data analysis under the supervision of K. T. K. M. E. prepared the first draft of the manuscript. All authors contributed to the study design, implementation, and interpretation of data, reviewed and revised the manuscript, and approved of the final draft.

The authors thank the study volunteers who participated in ALLRT/A5001 and HAILO/A5322, all the ACTG clinical units who enroll and follow participants, and the ACTG.

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Financial support. Research reported in this publication was supported by the National Institute of Aging (K23AG050260 to K. M. E.), the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (AI 036219 and 5UM01AI068634-10), the National Institute of Mental Health, and the National Institute of Dental and Craniofacial Research. This research was also supported by the Veterans Administration (VISN10 Geriatric Research Educational and Clinical Centers, Louis Stokes Cleveland Veterans Administration Medical Center to R. C. K.).

Potential conflicts of interest. K. M. E. and R. C. K. have received research funding to the University of Colorado and MetroHealth Medical Center, respectively, from Gilead Sciences, and K. M. E. has received consultant fees (paid to the University of Colorado) from Theratechnologies. F. J. P. is a consultant for and on the Speakers Bureau for Gilead Sciences, Janssen Pharmaceuticals, Merck and Co. and Bristol Myers Squibb. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Smit M, Brinkman K, Geerlings S, et al.; ATHENA observational cohort. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis **2015**; 15:810–8.
2. Erlandson KM, Allshouse AA, Jankowski CM, et al. Risk factors for falls in HIV-infected persons. J Acquir Immune Defic Syndr **2012**; 61:484–9.
3. Desquilbet L, Jacobson LP, Fried LP, et al. A frailty-related phenotype before HAART initiation as an independent risk factor for AIDS or death after HAART among HIV-infected men. J Gerontol A Biol Sci Med Sci **2011**; 66:1030–8.
4. Guaraldi G, Brothers TD, Zona S, et al. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. AIDS **2015**; 29:1633–41.
5. Greene M, Covinsky K, Astemborski J, et al. The relationship of physical performance with HIV disease and mortality. AIDS **2014**; 28:2711–9.
6. Piggott DA, Muzaale AD, Mehta SH, et al. Frailty, HIV infection, and mortality in an aging cohort of injection drug users. PLoS One **2013**; 8:e54910.
7. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA **2011**; 305:50–8.
8. Kooij KW, Wit FW, Schouten J, et al.; AGEhIV Cohort Study Group. HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls. AIDS **2016**; 30:241–50.
9. Smurzynski M, Collier AC, Koletar SL, et al. AIDS clinical trials group longitudinal linked randomized trials (ALLRT): rationale, design, and baseline characteristics. HIV Clin Trials **2008**; 9:269–82.
10. Newman AB, Gottdiener JS, Mcburnie MA, et al.; Cardiovascular Health Study Research Group. Associations of subclinical cardiovascular disease with frailty. J Gerontol A Biol Sci Med Sci **2001**; 56:M158–66.
11. Booth M. Assessment of physical activity: an international perspective. Res Q Exerc Sport **2000**; 71:S114–20.
12. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. AIDS **2007**; 21:1915–21.
13. Herr M, Robine JM, Aegerter P, Arvieu JJ, Ankri J. Contribution of socioeconomic position over life to frailty differences in old age: comparison of life-course models in a French sample of 2350 old people. Ann Epidemiol **2015**; 25:674–80.e1.
14. Soler-Vila H, García-Esquinas E, León-Muñoz LM, López-García E, Banegas JR, Rodríguez-Artalejo F. Contribution of health behaviours and clinical factors to socioeconomic differences in frailty among older adults. J Epidemiol Community Health **2016**; 70:354–60.