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Functional Status is Associated with Cardiovascular Disease and Diabetes in HIV+ Adults

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Background

- Many age-related chronic non-infectious diseases, such as cardiovascular disease, insulin resistance/diabetes mellitus, and chronic kidney disease, are more prevalent among persons living with HIV (PLWH) than in the general population.
- Frailty and disability occur earlier among PLWH than age-matched HIV-uninfected (HIV-) persons and contribute to mortality.
- Associations between frailty, disability, and other age-related chronic diseases are not well-characterized among PLWH. We hypothesize that such associations exist, therefore presence of frailty and disability in PLWH are important factors in risk stratification for other chronic diseases.

Methods

Population

- ACTG A5322 (HAILO: Long-Term Follow-up of Older HIV-infected Adults: Addressing Issues of Aging, HIV Infection and Inflammation) is an ongoing study of 1,035 PLWH (age **≥40 years)** that evaluates the long-term effects of treated HIV on chronic inflammation and incidence of non-AIDS clinical events among older PLWH. Baseline characteristics are presented in Table 1.
- Functional status was evaluated at baseline (study entry) by measuring frailty using **Fried's** criteria and disability by any impairment in Instrumental Activities of Daily Living (IADL).

Table 1: Baseline demographic and clinical characteristics

Variable	Percent*, N = 1035
Age, N (IQR)	51 (10)
Male sex	81
Race/Ethnicity	
White, non-Hispanic	48
Black, non-Hispanic	29
Hispanic, other	23
Frail/pre-frail	44
IADL impairment	17
BMI, Median (IQR)	27.2 (6.8)
Smoking status	
Never	41
Former	34
Current	25
Alcohol use**	
No use	40
Light/Moderate use	43
Heavy use	17
Diabetes	12
Chronic kidney disease	10
Hypertension	59
Hyperlipidemia	87
Positive HCV serology	12
HIV clinical characteristics	
Nadir CD4, median (IQR)	228 (285)
ART duration, years, median (IQR)	7.8 (7.5)
PLWH whose HIV RNA (viral load) was suppressed ≥75% of the time pre-enrollment	76
History of clinical AIDS	21

IADL=Instrumental Activities of Daily Living; BMI=body mass index; HCV= hepatitis C virus; ART=antiretroviral therapy
*Unless otherwise specified, **Light/moderate use: 1-14 drinks/week (men), 1-7 drinks/week (women); heavy use: >14 drinks/week (men), >7 drinks/week (women)

Methods (continued)

Clinical Events

- Fatal and non-fatal clinical events (Table 2) were recorded for each participant after study enrollment.
- Follow-up: from time of study enrollment to the date of the first-occurring event, date of death, or date of the most recent study visit (for persons who did not experience a clinical event)
- We calculated rates of non-fatal events and cause-specific mortality (Table 2).

Statistics

- Poisson regression models:
  - To identify risk factors for occurrence of any fatal and non-fatal clinical events of interest, and also for specific individual events with sufficient sample size
  - To assess effect modification of race, gender and sex on specific risk factors (frailty, disability) and fatal/non-fatal events
  - All factors with p-value <0.05 in univariable models were entered into the multivariable model; factors with p-value >0.1 in the multivariable model were excluded from the final model.

Table 2: Rates of non-fatal and fatal events

Event type	Non-fatal events: N, rate per 100 person-years (95% CI)	Fatal events: N, rate per 100 person-years (95% CI)
Cardiovascular disease-specific events • **Includes coronary artery disease, myocardial infarction, stroke/transient ischemic attack, angina, peripheral arterial disease, cardiomyopathy/heart failure, arrhythmia, deep vein thrombosis, pulmonary embolism**	49, 1.55 (1.15-2.05)	9, 0.28 (0.13-0.53)
Non-AIDS defining cancer-specific events	16, 0.5 (0.28-0.81)	5, 0.15 (0.05-0.36)
Liver disease-specific events • **Includes cirrhosis, hepatic steatosis**	8, 0.25 (0.11-0.49)	2, 0.06 (0.01-0.22)
Non-AIDS infection • **Includes bacterial deep tissue/body cavity infection, influenza, bacterial pneumonia, pyelonephritis, bacteremia, varicella zoster**	39, 0.23 (0.87-1.68)	1, 0.03 (0-0.17)
Diabetes-specific events	68, 2.46 (1.91-3.12)	---
Chronic kidney disease-specific events	14, 0.48 (0.26-0.81)	---
Bone disease-specific events • **Includes fracture, avascular necrosis, osteopenia, osteoporosis**	48, 1.52 (1.12-2.02)	---
Joint disease-specific events • **Includes degenerative joint disease, reactive arthritis**	21, 0.66 (0.41-1.01)	---
Pulmonary disease-specific events • **Includes chronic obstructive pulmonary disease, pulmonary hypertension**	3, 0.09 (0.02-0.27)	---
Neurocognitive disease-specific events	29, 0.91 (0.61-1.3)	---
Depression-specific events	53, 1.69 (1.27-2.21)	---
All events	277, 10.11(8.95-11.37)	26, 0.80(0.52-1.17)

Results

Table 3: Adjusted associations between demographic, behavioral and clinical variables and cardiovascular events

Variable	Referent variable	IRR (95% CI)	p-value
Baseline age, per each 10-year increase	---	1.46 (1.08 – 1.97)	**0.01**
Baseline pre-frailty	Non-frail	2.02 (1.04 – 3.95)	**0.04**
Baseline frailty	Non-frail	5.13 (2.18 – 12.10)	**<0.001**
Viral load suppression pre-event	Suppression <75% of the time	0.41 (0.21 – 0.79)	**0.007**
Years of TDF use prior to event per one year increase	--	0.91 (0.84 – 0.98)	**0.02**
History of DM prior to event	No history of DM	2.76 (1.53 – 4.96)	**<0.001**

IRR=incidence rate ratio; TDF=tenofovir disoproxil fumarate; DM=diabetes mellitus
Variables not associated with cardiovascular events: sex, education level, medical insurance status, likely HIV transmission route, change in frailty score from baseline, baseline IADL impairment, change in IADL score from baseline, pre-ART HIV RNA, pre-ART CD4+ T-cell count, CD4+ T cell count prior to event, baseline BMI, change in BMI from baseline, baseline waist circumference, baseline smoking status, smoking status prior to event, frequency of alcohol drinking at baseline/prior to event, binge-drinking at baseline/prior to event, years of ART before baseline, still taking initial ART regimen, protease inhibitor use prior to event, years of protease inhibitor use prior to event, history of hypertension prior to event, history of hyperlipidemia prior to event, history of positive hepatitis C serology prior to event, history of renal disease prior to event, history of bone disease prior to event

Table 4: Adjusted associations between demographic, behavioral and clinical variables and incident diabetes mellitus

Variable	Referent variable	IRR (95% CI)*	p-value*	IRR (95% CI)**	p-value**
Race/ethnicity	White, non-Hispanic				
Black, non-Hispanic		1.07 (0.56, 2.05)	0.8	1.21 (0.66 – 2.22)	0.5
Hispanic, other		2.10 (1.19, 3.68)	**0.01**	2.14 (1.23 – 3.69)	**0.007**
Baseline pre-frailty	Non-frail	---	**---**	1.30 (0.79 – 2.14)	0.3
Baseline frailty	Non-frail	---	**---**	2.83 (1.23 – 6.47)	**0.01**
Baseline IADL impairment	No IADL impairment	2.03 (1.17, 3.54)	**0.01**	---	**---**
Moderate/heavy alcohol drinking prior to event	Abstention/light drinking	0.32 (0.14, 0.75)	**0.008**	0.33 (0.14 – 0.75)	**0.009**
History of hyperlipidemia prior to event	No history of hyperlipidemia	6.88 (0.94, 50.56)	0.06	7.60 (1.03 – 55.87)	**0.05**
History of positive HCV serology	No history of positive HCV serology	0.33 (0.11, 1.02)	**0.05**	0.33 (0.10 – 1.05)	0.06

IRR=incidence rate ratio; IADL=Instrumental Activities of Daily Living; HCV=hepatitis C virus
*Final model with IADL impairment as a predictor
**Final model with frailty/pre-frailty as predictor
Variables not associated with diabetes: sex, baseline age, education level, medical insurance status, likely HIV transmission route, baseline frailty/pre-frailty, change in frailty score from baseline, change in IADL score from baseline, pre-ART HIV RNA, proportion of time with HIV RNA <200 copies/mL, pre-ART CD4+ T-cell count, CD4+ T cell count prior to event, baseline BMI, change in BMI from baseline, baseline waist circumference, baseline smoking status, smoking status prior to event, binge-drinking at baseline/prior to event, years of ART before baseline, still taking initial ART regimen, years of protease inhibitor use prior to event, TDF use prior to event, years of TDF use prior to event, history of hypertension prior to event, history of renal disease prior to event, history of bone disease prior to event

Table 5: Effect modification by demographic factors on association between frailty status and occurrence of cardiovascular events

Variable*	IRR (95% CI)	p-value
Effect of race on association between frailty and occurrence of cardiovascular events		
Frailty/pre-frailty among white participants	1.40 (0.53 – 3.70)	0.5
Frailty/pre-frailty among black participants	5.24 (1.52 – 18.1)	**0.009**
Frailty/pre-frailty among Hispanic/other participants	1.66 (0.42 – 6.46)	0.5
Effect of sex on association between frailty and occurrence of cardiovascular events		
Frailty/pre-frailty among women	3.37 (0.40 – 28.2)	0.3
Frailty/pre-frailty among men	2.55 (1.31 – 4.97)	**0.006**
Effect of age on association between frailty and occurrence of cardiovascular events		
Frailty/pre-frailty among those <50 years	1.27 (0.34 – 4.73)	0.7
Frailty/pre-frailty among those 50 - 59 years	3.66 (1.37 – 9.82)	**0.01**
Frailty/pre-frailty among those ≥60 years	1.86 (0.56 – 6.15)	0.3

IRR=incidence rate ratio
*Referent variable: non-frail
p-value of interaction between race and frailty = 0.183
p-value of interaction between sex and frailty = 0.792
p-value of interaction between age and frailty = 0.397
Final models adjusted for baseline age, frailty/pre-frailty, proportion of time with VL<200 copies/mL prior to event, years of TDF use prior to event, and history of diabetes prior to event

Summary

- Frail/pre-frail status was associated with cardiovascular events. There was evidence that this association was strongest among black, non-Hispanic PLWH, although this effect modification was not statistically significant.
- Disability was associated with incident diabetes, regardless of race.
- No effect modification by sex or age on the associations between either frailty or disability and cardiovascular events or diabetes was evident.

Conclusions

- Frailty and disability were common and associated with significantly elevated risk for cardiovascular events and incident diabetes, respectively.
- Routinely assessing functional status in aging PLWH may optimize risk stratification for these serious co-morbid conditions.