Frequency, Risk Factors, and Mediators of Frailty Transitions During Long-Term Follow-Up Among People With HIV and HIV-Negative AGE$_h$IV Cohort Participants

Eveline Verheij, MD,[a,b] Ferdinand W. Wit, MD, PhD,[a,b,c] Sebastiaan O. Verboeket, MD,[a,b]
Maarten F. Schim van der Loeff, MD, PhD,[d,e] Jeannine F. Nellen, MD, PhD,[a]
Peter Reiss, MD, PhD,[a,b,c] and Gregory D. Kirk, MD, PhD[f]

Background: We previously demonstrated a higher prevalence of frailty among AGE$_h$IV-cohort participants with HIV (PWH) than among age- and lifestyle-comparable HIV-negative participants. Furthermore, frailty was associated with the development of comorbidities and mortality. As frailty may be a dynamic state, we evaluated the frequency of transitions between frailty states, and explored which factors were associated with transition toward frailty in this cohort.

Methods: The study enrolled 598 PWH and 550 HIV-negative participants aged ≥45 years. Of those, 497 and 479 participants, respectively, participated in ≥2 consecutive biennial study-visits between October 2010 and October 2016, contributing 918 and 915 visit-pairs, respectively. We describe the frequency, direction, and risk factors of frailty transitions. Logistic regression models with generalized estimating equations were used to evaluate determinants for transition to frailty, including HIV-status, socio-demographic, behavioral, HIV-related factors, and various inflammatory and related biomarkers.

Results: Transitioning between frailty states in any direction occurred in 36% of a total of 1833 visit-pairs. The odds of nonfrail participants transitioning toward frailty were significantly higher for PWH, occurring in 35 PWH (7.3%) and 25 (5.2%) HIV-negative nonfrail participants, respectively (odd ratio$_{HIV}$ 2.19, 95% confidence interval 1.28 to 3.75). The increased risk among PWH was attenuated when sequentially adjusting for waist–hip ratio, number of pre-existent comorbidities, and the presence of depressive symptoms.

Conclusion: PWH are at increased risk of transitioning to frailty, and thereby at increased risk of adverse health outcomes. Whether optimizing the management of obesity, comorbidity, or depressive symptoms may modify the risk of becoming frail requires further investigation.

Key Words: frailty, HIV, transitions, comorbidities, depression

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INTRODUCTION

For people living with HIV (PWH) with access to combination antiretroviral therapy (cART), HIV-infection has become a chronic condition, and as they continue to age, comorbidities have become the primary causes of morbidity and mortality in this population.[1]

Frailty is conceptualized as a state of decreased physical resilience because of deficits across multiple organ systems,

which increases the vulnerability for adverse health outcomes such as falls, hospitalization, disability, and death.[2,3] In a previous cross-sectional analysis of the AGE$_h$IV cohort, we showed that PWH had a higher prevalence of frailty compared with HIV-negative persons with similar risk characteristics. Among PWH, parameters related to body-composition, including higher waist-to-hip-ratio (WHR), were most strongly independently associated with frailty.[4] Moreover, in a subsequent analysis, we found that in our study population with a median age of 52.7 years [inter-quartile range (IQR) 48.2–59.3], frailty was predictive of both incident comorbidity and mortality, independent of traditional risk factors such as age, comorbidity burden, and tobacco or alcohol use.[5]

Previous studies have shown frailty to be a dynamic state, in which participants can bidirectionally transition between frailty states (robust, prefrail, and frail).[6,7] A better understanding of which factors predict a transition to the frailty phenotype, including those which are HIV-specific, may help to both identify PWH at risk and identify potentially modifiable underlying risk factors. In the current analysis, we extend our previous findings over a longer period of observation to (1) compare the frequency and direction of transitions between frailty states among both PWH and HIV-negative AGE$_h$IV participants, (2) determine which factors mediate any observed differences between PWH and HIV-negative participants, and (3) evaluate which factors predict transition to frailty and back, independently of HIV-infection.

METHODS

Study Population

The AGE$_h$IV Cohort Study enrolled 598 PWH from the HIV outpatient clinic of the Amsterdam University Medical Centers and 550 HIV-negative participants from either the sexual health clinic or the Amsterdam Cohort Studies on HIV/AIDS at the Public Health Service in Amsterdam, the Netherlands.[8] As described previously,[9] participants were included if they were ≥45 years old at time of enrolment. The recruitment of HIV-negative participants resulted in a highly comparable control group regarding sociodemographic and lifestyle-related behavioral characteristics, including sexual risk behavior.[9] For the current analysis, we used data collected from up to 3 biennial study-visits between October 2010 and October 2016. Written informed consent was obtained from all participants. The study protocol was approved by the Amsterdam UMC ethics committee, and is registered at www.ClinicalTrials.gov under identifier NCT01466582.

Outcome Definition

Frailty was assessed during each study-visit, as previously described by Kooij et al.[4] Briefly, the Fried frailty phenotype encompasses 5 domains, each scored as absent or present: (1) unintentional weight loss, (2) low physical activity, (3) exhaustion, (4) decreased grip strength, and (5) slow gait speed (for definitions see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B551). The pres-

ence of a frailty score of 3 or higher denotes frailty, 1–2 prefrailty, and 0 robustness. We did not calculate a frailty score if data on more than 2 domains were missing (n = 14 in 3022 study-visits; <0.5%). If data on one (n = 102 in 3008 study-visits; 3.4%) or 2 (n = 7; 0.2%) frailty domains were missing, we assumed these domains to be normal.

Statistical Analysis

As our analysis focused on the frequency of transition between frailty states, participants were included only if data were available from at least 2 consecutive study-visits (ie, v1 and v2; or v2 and v3; but not v1 and v3). Baseline characteristics of PWH and HIV-negative participants (the study groups) included in the analysis were compared using Wilcoxon rank-sum test, ANOVA, and χ^2 test as appropriate (Table 1). We first determined the frequency of transitions in any direction between frailty states (ie, between robust, prefrail, and frail) during follow-up within each study group.

To determine which factors may mediate observed differences between PWH and HIV-negative participants in predicting a transition to frailty, we compared participants who became frail (ie, transitioned from robust/prefrail to frail) to participants who remained robust during 2 consecutive study-visits. By excluding participants who remained prefrail at both visits, we maximized the contrast between those who remained robust and those who transitioned to frailty, as prefrailty is an intermediate state with intermediate risk for adverse health outcomes.[5] Factors associated with prefrailty may weaken the association between remaining robust or transitioning to frailty. Potential confounding or mediating variables were explored for their univariate association with transition to frailty, and included HIV-status, socio-demographics, body-composition measures, risk behaviors, prevalent comorbidities and biomarkers of chronic inflammation, coagulation, microbial translocation, and immune activation.

Because participants were allowed to contribute data to the analyses twice (ie, from v1 to v2 and v2 to v3), logistic regression models with generalized estimating equations were used to adjust for within-participant correlation. Multivariable logistic regression models were built, using a step-wise forward variable selection procedure, assessing all variables with a univariate association with transitioning to frailty at a P-value of <0.2. Gender and HIV risk group were highly correlated and were not estimable when each was included separately in models. Therefore, sexual risk group was created as a composite variable of gender and sexual behavior (that is, men who have sex with men (MSM), heterosexual male, and female). Age, sexual risk group, non-white ethnicity and level of education were forced into models based on a priori knowledge (model A). As the key covariate of interest, HIV-status was forced into all models. Explanatory variables were retained in the multivariable model if they attenuated the HIV-coefficient by at least 10% or if they remained statistically significantly ($P < 0.05$) associated with transition to frailty (model B). In addition, we explored factors associated with transitioning back from frailty to prefrail/robust, using those remaining frail as the reference group.

TABLE 1. Baseline Characteristics of Participants, Stratified by HIV Status

Sociodemographic	HIV-Positive, n = 497, n (%) or median (IQR) or mean (SD)	HIV-Negative, n = 479, n (%) or median (IQR) or mean (SD)	P
Age, yrs	53.3 (48.3–59.6)	52.3 (48.1–58.6)	0.15*
Risk group, n (%)			0.10†
MSM male	386 (77.7)	344 (71.8)	
Non-MSM male	57 (11.5)	65 (13.6)	
Female	54 (10.9)	70 (14.6)	
Missing	0 (0)	0 (0)	
Ethnicity, n (%)			<0.001†
Non-white ethnicity	50 (10.1)	16 (3.3)	
White ethnicity	447 (89.9)	463 (96.7)	
Missing	0 (0)	0 (0)	
Education			<0.001†
Higher educational attainment‡	199 (40.0)	268 (56.0)	
Lower educational attainment	266 (53.5)	198 (41.3)	
Missing	32 (6.4)	13 (2.7)	
Behavior			
Smoking status, n (%)			0.01†
Never	160 (32.2.3)	182 (38.0)	
Former	159 (32.0)	177 (37.0)	
Current	160 (32.2)	117 (24.4)	
Missing	18 (3.6)	3 (0.6)	
Pack years (if ever smoked)	22.2 (7.6–36.8)	13.9 (4.0–28.5)	<0.001§
Heavy-daily alcohol use past 6 mo, n (%)‖	17 (3.4)	34 (7.1)	0.003†
Binge drinking, n (%)¶	92 (18.5)	154 (32.2)	<0.001†
Injection drug use (ever), n (%)	16 (3.2)	4 (0.8)	<0.001†
THC use during last 6 mo, n (%)	47 (10.2)	37 (7.9)	0.22†
Physically active, n (%)#	201 (40.5)	252 (52.6)	<0.001†
Body composition			
Waist-circumference, cm	93.4 (10.4)	92.0 (10.9)	0.034*
Hip-circumference, cm	96.5 (7.1)	99.9 (6.9)	<0.001*
Waist-to-hip ratio	0.97 (0.07)	0.92 (0.08)	<0.001*
Body-mass index, kg/m^2	24.5 (3.5)	25.2 (3.6)	0.004*
Comorbidities, n (%)			
No. of age-associated comorbidities**			<0.001†
0	238 (48.0)	299 (62.4)	
1	153 (30.9)	131 (27.4)	
≥2	105 (21.2)	49 (10.2)	
Hepatitis B virus DNA positive	29 (5.8)	3 (0.6)	<0.001†
Hepatitis C virus RNA positive	11 (2.2)	5 (1.0)	0.15†
Cytomegalovirus IgG positive	465 (93.8)	368 (76.8)	<0.001†
Depressive symptoms††			0.001†
CES-D ≤ 8	271 (54.5)	328 (68.5)	
CES-D > 8 < 16	105 (21.1)	76 (15.9)	
CES-D ≥16	89 (17.9)	65 (13.6)	
Missing	32 (6.4)	10 (2.1)	
Biomarkers			
hsCRP, mg/L	1.4 (0.7–3.1)	1.0 (0.6–2.0)	<0.001§
D-dimer, mg/L	0.2 (0.2–0.3)	0.3 (0.2–0.4)	0.002§
IL-6, pg/mL	1.5 (1.0–2.8)	1.9 (1.2–3.1)	<0.001§
sCD14, ng/mL	1562 (1310–1963)	1361 (1082–1745)	<0.001§
sCD163, ng/mL	287 (207–411)	248 (183–345)	<0.001§
I-FABP, ng/mL	2.2 (1.4–3.7)	1.1 (0.7–1.6)	<0.001§
Frailty score, n (%)			<0.001†
Robust	181 (36.5)	292 (61.0)	
Prefrail	260 (52.4)	174 (36.3)	

TABLE 1. (*Continued*) Baseline Characteristics of Participants, Stratified by HIV Status

Sociodemographic	HIV-Positive, n = 497, n (%) or median (IQR) or mean (SD)	HIV-Negative, n = 479, n (%) or median (IQR) or mean (SD)	P
Frail	55 (11.1)	13 (2.7)	
Years since HIV- diagnosis	12.2 (6.7–17.3)	—	—
CD4 cell count			
Nadir CD4 count, cells/μL	170.0 (70.0–260.0)	—	—
Mean CD4 in 12 months before enrolment, cells/μL	565.0 (434.2–740.0)	—	—
Cumulative time spent at CD4 count <200 cells/μL, yrs	0.1 (0.0–0.9)	—	—
CD4/CD8 ratio at enrolment	0.7 (0.5–1.0)	—	—
History of CDC class C AIDS defining diagnosis, n (%)	157 (31.7)	—	—
Using cART at enrolment, n (%)	474 (95.4)	—	—
Cumulative exposure to ART, yrs	10.7 (4.4–14.6)	—	—
ART-experienced before starting cART, n (%)	103 (21.7)	—	—
Having used zalcitabine, n (%)	47 (9.5)	—	—
Duration of zalcitabine use, yrs‡‡	0.7 (0.3–1.6)	—	—
Having used didanosine, n (%)	169 (28.3)	—	—
Duration of didanosine use, yrs§§	2.7 (0.9–6.9)	—	—
Having used stavudine, n (%)	216 (36.1)	—	—
Duration of stavudine use, yrs‖‖	3.5 (1.6–5.5)	—	—
Having used zidovudine, n (%)	358 (59.9)	—	—
Duration of zidovudine use, yrs¶¶	3.6 (1.3–7.1)	—	—
HIV-RNA <200 c/mL in year before enrolment, n (%) ##	450 (95.1)	—	—
Cumulative duration of HIV-RNA <200 c/mL, yrs##	8.8 (3.8–12.7)	—	—

Significant at $P < 0.05$.

*ANOVA.

†Pearson's χ^2 test.

‡Higher education; attained at least a bachelor's degree.

§Kruskal–Wallis test.

‖Heavy daily alcohol defined as >5 alcohol units almost daily for a man and >4 units almost daily for a woman during the last 6 months.

¶Binge alcohol defined as >6 alcohol units a day, at least once per month during the last 6 months.

#Being physically active was defined following the Dutch guidelines for healthy physical activity ("Combinorm"): at least 5 days per week at least 30 minutes of moderate physical activity or at least 3 days per week at least 20 minutes of heavy physical activity.

**Comorbidities included are chronic obstructive pulmonary disease or asthma (defining obstruction as an FEV_1/FVC-ratio z-score < -1.64 using Global Lung Initiative reference calculations), diabetes [HbA1c $\geq$ 48 mmol/mol and/or elevated blood glucose (nonfasting $\geq$ 11.1 mmol/L or fasting $\geq$ 7.0 mmol/L) or on antidiabetic medication], hypertension (use of antihypertensive medication or measured grade 2 hypertension following European Guidelines systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg in all 3 measurements), decreased kidney function (eGFR <60 mL/min/1.73 m²) based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, osteoporosis (having a T score of -2.5 SD or lower, in men aged <50 years and premenopausal women; a Z score of -2 SD or lower in men aged $\geq$50 years and postmenopausal women), self-reported and validated heart-failure, non-AIDS associated cancer (excluding nonmelanoma skin cancers), and cardiovascular disease (myocardial infarction, angina pectoris, peripheral artery disease, ischemic stroke, and/or transient ischemic attack).

††CES-D scale, with 2 questions used in the frailty scale excluded from CES-D score calculation.

‡‡For those who had used zalcitabine.

§§For those who had used didanosine.

‖‖For those who had used stavudine.

¶¶For those who had used zidovudine.

##If currently on cART.

ART, antiretroviral therapy; CDC, centers for disease control and prevention; THC, tetrahydrocannabinol.

Most variables were time-updated, and added to the model according to their value at time of the first of the consecutive study-visit pair, as the main interest was the predictive value of those variables. Other variables were time-fixed and only measured at enrolment [ie, cytomegalovirus serology, hepatitis B and C virus serology, and plasma levels of intestinal fatty acid-binding protein (I-FABP), interleukin-6 (IL-6), soluble CD14 (sCD14), and soluble CD163 (sCD163)], as biomarkers of intestinal permeability, inflammation, and innate immune activation, respectively. Levels of high-sensitivity C-reactive protein (hsCRP) and D-dimer were measured at each study visit.

As there is a bidirectional relationship between frailty and having depressive symptoms (ie, frailty can lead to depressive symptoms and vice versa) and these variables are partly collinear [certain center for epidemiologic studies depression scale (CES-D) items overlap with items to assess frailty], we created 2 separate final models: one with and one without adjustment for depressive symptoms (model C and D). Depressive symptoms were categorized as $\leq$8, >8 but <16, or $\geq$16 points on the CES-D scale, after exclusion of 2 items in the CES-D that are part of the frailty assessment of exhaustion ("Everything you did was an effort?" and "I could not get going"). Interactions between variables were explored,

and considered statistically significant when $P \leq 0.1$. These interactions were evaluated in the multivariable model before depression was added.

Two sensitivity analyses were performed:(1) in which participants were excluded if they experienced transition to frailty because of a change in only one component of the frailty score, thus emphasizing participants who experienced more substantial declines in their health status; and (2) in which participants who remained prefrail at both consecutive study-visits were included in the reference group.

Finally, we explored factors predictive of transition to frailty, including those that are HIV-specific, in an analysis restricted to PWH. Following a similar step-wise forward variable selection procedure, a multivariable model was built to determine factors independently predictive of transitioning to frailty among PWH. Variables that had been identified as being associated with transition to frailty in the final model that included all study participants, were forced into this model.

All reported *P* values are 2-sided. We used Stata version 15 (StataCorp LP; College Station, TX) for the statistical analysis.

RESULTS

Baseline Characteristics

In total, 497 PWH and 479 HIV-negative participants contributed 915 and 918 consecutive visit-pairs, respectively. Baseline characteristics of participants included in the analysis are shown in Table 1, stratified by HIV-status. At cohort enrolment, participants overall had a median age of 52.7 years, (IQR 48.2–59.3 years) and 74.8% were MSM and these factors did not differ by HIV-status. PWH were more often current smokers and smoked more intensely, reported less problematic alcohol use, reported more often depressive symptoms, had higher WHR but lower BMI, and were diagnosed with more comorbidities. Most (95.4%) PWH were on cART, of whom 95.1% were virally suppressed (viral load <200 copies/mL) in the year before enrolment. Median duration since diagnosis of HIV infection was 12.2 years.

Transitions Between Frailty Phenotypes

Transitions did not occur in 1174 of the total 1833 visit-pairs (64%): 682 visit-pairs (37% of total) remained robust, 449 (25%) visit-pairs remained prefrail, and 43 (2%) visit-pairs remained frail. In the remaining 659 (36%) visit-pairs in which transitions did occur, 305 (46.0%) were in the direction of frailty (from robust/prefrail to prefrail/frail) and 354 (54.0%) in the direction of robustness (from prefrail/frail to robust/prefrail). For both PWH and HIV-negative participants (Fig. 1), direct transitions in either direction between the robust and frail states were very infrequent (<0.8% for any). In contrast, transitions occurred most frequently between the robust and prefrail states (29% of all transitions). During study follow-up, 35 (3.8%) PWH and 25 (2.7%) HIV-negative participants transitioned to frailty, respectively. For those transitioning to frailty, most were prefrail at the

previous study-visit (Fig. 1). Of all participants who were classified as frail during at least one study visit, most of them did so during only a single study visit (78.7%) with most transitioning back to the prefrail state. Thirty-eight deaths were observed overall, with a greater proportion among PWH compared with HIV-negatives (5.2% versus 1.3%).

Factors Associated With Transition to Frailty

Our primary comparison groups included visit-pairs where participants transitioned to frailty (n = 60, 8.1% of total visit-pairs) compared with visit-pairs where participants remained robust (n = 682, 91.9%) as the reference group (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B551 for descriptive characteristics of these visit-pairs).

In unadjusted analyses, HIV-positive status was associated with a >2-fold higher odds [odd ratio (OR_{HIV}) 2.19, 95% confidence interval (CI): 1.28 to 3.75, $P = 0.004$] of transitioning to frailty (Fig. 2). In multivariable models, this association was increasingly attenuated after stepwise adjustment for sociodemographic factors (OR_{HIV} 2.05, 95% CI: 1.16 to 3.63, $P = 0.014$), WHR (OR_{HIV} 1.82, 95% CI: 0.97 to 3.39, $P = 0.06$), and no longer significant after additional adjustment for number of pre-existing comorbidities (OR_{HIV} 1.57, 95% CI: 0.83 to 2.97, $P = 0.16$) and depressive symptoms (OR 1.27, 95% CI: 0.65 to 2.50; $P = 0.48$) (Fig. 2, see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B551). Concerning WHR, the attenuation was less after adjusting for waist-circumference (OR_{HIV} 2.15, 95% CI: 1.19 to 3.85, $P = 0.01$) than for hip-circumference (OR_{HIV} 1.93, 95% CI: 1.08 to 3.45, $P = 0.03$). Higher age, higher number of comorbidities, and having depressive symptoms, were each independently associated with transition to frailty in the multivariable models (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/B551). Other variables, including each of the biomarkers we assessed, did not attenuate the OR_{HIV} for transitioning to frailty, nor were they themselves significantly independently associated with such transition. However, hs-CRP, D-dimer, and I-FABP were associated with transition to frailty in unadjusted models. After adjusting for sociodemographic variables, D-dimer and I-FABP were no longer associated with transitioning to frailty. High-sensitivity CRP remained associated with transitioning to frailty after adjusting for socio-demographics and waist-to-hip-ratio, but lost significance after adjusting for the prevalent number of comorbidities. No interactions were observed between variables in the final model; however, when re-introducing the different components of the waist-to-hip-ratio separately, a significant interaction between hip-circumference and HIV-status was observed (*P*-interaction = 0.01). For PWH, the OR for transitioning to frailty for each centimeter smaller hip-circumference was significant (OR 1.08, 95% CI: 1.02 to 1.14, $P = 0.006$), but not for HIV-negative participants (OR 0.96, 95% CI: 0.90 to 1.03, $P = 0.275$).

Factors associated with transitioning back toward robustness were also explored. This analysis included visit-pairs where participants transitioned from frailty toward
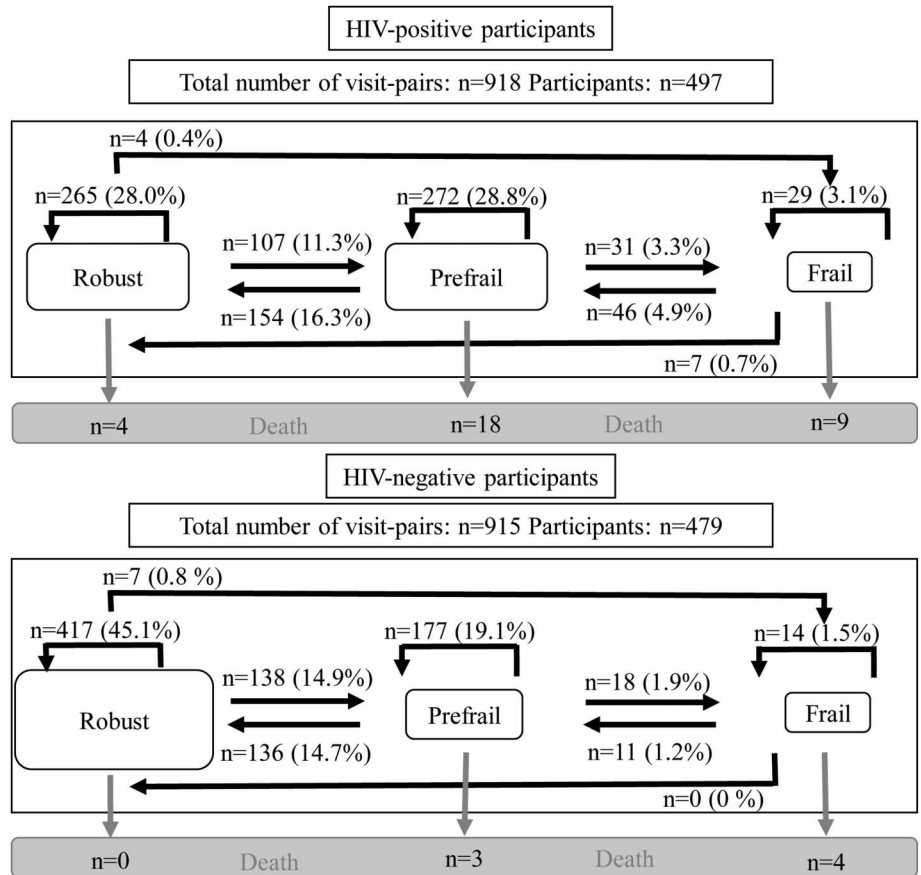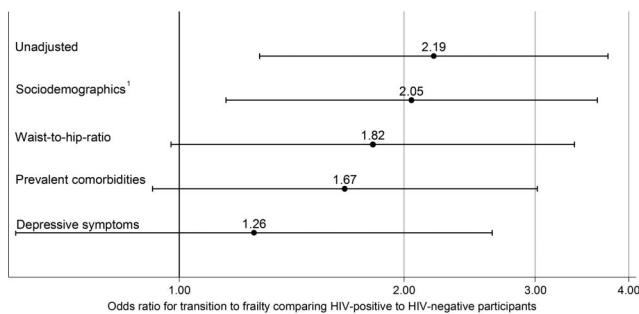
FIGURE 1. Frequency of frailty phenotype transitions during follow-up, stratified by HIV-status.

robustness (prefrail/robust) (n = 64, 3.5% of total visit-pairs) with visit-pairs where participants remained frail (n = 43, 2.3%) serving as the reference group. In unadjusted analysis, older age, a higher number of prevalent comorbidities, and higher level of depression were associated with lower odds of transitioning back from frailty (see Table 4, Supplemental Digital Content, http://links.lww.com/QAI/B551). In multi-variable analysis, having a higher number of prevalent comorbidities resulted in a lower OR to transition to robustness (OR 0.22, 95% CI: 0.06 to 0.81, *P* = 0.023) (see

FIGURE 2. Association of HIV-status with transition to frailty; step-wise forward adjustments for potential mediating factors. Results are based on logistic regression models with generalized estimating equations. [1]Adjusted for age, sexual risk group, non-white ethnicity, and level of education.

Table 4, Supplemental Digital Content, http://links.lww.com/QAI/B551, model C).

All other variables, were not associated with transitioning to robustness nor attenuated the HIV effect, and were therefore excluded from the final model. No interactions were observed in the final model (model C). Both sensitivity analyses (ie, the first restricted to participants who transitioned to frailty by an increase in the frailty score with at least 2 points, and the second which included participants who remained prefrail at consecutive study-visits along with stably robust participants in the reference group) yielded similar results (data not shown).

Stratified Analysis Among PWH Only

Exploration of HIV-related factors among PWH showed independently higher odds for transitioning to frailty among participants with a longer cumulative exposure to (square root transformed) zalcitabine (ddC) (OR 2.15, 95% CI: 1.02 to 4.54, *P* = 0.045), while adjusting for age, WHR, and number of prevalent comorbidities (see Table 5, Supplemental Digital Content, http://links.lww.com/QAI/B551).

Other HIV-associated factors, including CD4 nadir, and prior use or duration of exposure to nucleoside analogues, other than ddC, were not associated with transitioning to frailty.

DISCUSSION

In an earlier analysis from our AGE$_h$IV cohort, we reported a significantly higher prevalence of frailty among PWH.[4] We now extend these findings by demonstrating that PWH also are more likely to become frail during long-term follow-up.

Of note, during the 3 study-visits with 2-year intervals between study-visits, transition to frailty was infrequent and most visit-pairs were nontransitional.[10] When transitions between frailty phenotypes did occur, they were mostly among adjacent frailty phenotypes (eg, from robust to prefrail), similar to what has been observed in other studies.[6,10] PWH tended to experience slightly more transitions compared with HIV-negative participants, partly explained by HIV-negative participants more often remaining robust and partly because the previously mentioned higher likelihood for PWH to transition to frailty. Importantly, for most participants assessed as being frail, this was the case only once during the study period. We cannot rule out that this may reflect an imprecision of the instrument to assess frailty in our cohort of middle-aged participants. In addition, frailty transitions may have gone unrecognized, given that frailty was only biennially assessed. Nonetheless, despite its dynamic character, we have previously shown that frailty was a strong predictor of mortality and incident comorbidity, with those who were prefrail being at intermediate risk for both outcomes.[5]

The association between HIV-positive status and an increased odds of transitioning to frailty was largely mediated by adjustment for a higher waist-to-hip-ratio, a higher number of prevalent comorbidities and a higher prevalence of depressive symptoms among PWH. These findings largely resemble those we have reported previously for participants at time of entry into the cohort.[4]

Apart from the known association between abdominal obesity and frailty in the general population,[11–13] highly treatment-experienced PWH may develop persistent lipoatrophy and sarcopenia as a result of past exposure to thymidine analogues and/or severe HIV disease, features which may also contribute to the development of frailty. The increased waist-to-hip-ratio among PWH that we observed is the result of both an increased waist circumference and a smaller hip circumference compared with the HIV-negative participants, consistent with these well-characterized body-composition changes among PWH.[14] Notably, waist–hip ratio was not significantly associated with transitioning to frailty, but did seem to mediate the HIV effect. In further support of the differential body-composition hypothesis among PWH, we demonstrated that smaller hip-circumference, as possible proxy for lipoatrophy, was significantly associated with frailty only among PWH but not among our HIV-negative participants.

The AGE$_h$IV cohort represents a highly treatment-experienced population of PWH with the prolonged duration of HIV infection, lengthy exposure to ART, and excellent levels of viral suppression. In addition to WHR, we observed that PWH that historically used zalcitabine had higher odds of transitioning to frailty body-composition. This finding should be interpreted with caution, as we could not find an association of transitioning to frailty with prior use of other toxic nucleoside-analogue reverse transcriptase inhibitors such as didanosine, stavudine, and zidovudine nor with duration of prior severe immunosuppression or having had AIDS.

The presence of a higher number of prevalent comorbidities was also independently associated with an increased likelihood of transitioning to frailty.[10] Importantly, the presence of multiple comorbidities was also independently associated with a reduced likelihood to transition back toward robustness, similar to what was recently shown in the ALIVE cohort.[10] We have previously shown in this same cohort that participants who are frail have a higher probability to develop one or more incident comorbidities,[5] which together with the results from other studies[3,15,16] suggests a complex bidirectional interplay between frailty and comorbidity. That said, frailty did also develop in some individuals without any overt comorbidity (n= 19, ie, 32% of those who transitioned to frailty; indifferent by HIV-status, $P = 0.143$), supporting the concept of frailty as an overall decline in multiple organ systems, which is not necessarily simply a direct consequence of the number of comorbidities.

As was the case for the number of prevalent comorbidities, having depressive symptoms both attenuated the association between HIV-positive status and transitioning to frailty, and was itself independently associated with transition to frailty, confirming results from the WIHS[17] and MACS HIV cohort studies.[15] These results underline the need for proper attention to symptoms of depression in the care of PWH, not only to improve mental health but potentially also to help ensure current and future physical health.

In view of persistent inflammation in PWH having been hypothesized to be associated with adverse age-related outcomes, including frailty,[18–21] we also explored whether biomarkers of inflammation, coagulation, microbial translocation, and immune activation were associated with transitioning to frailty. Prior data are limited to a single longitudinal study, which demonstrated an increase in inflammatory index associated with frailty was predictive of both frailty progression, whereas reduced inflammation was associated with frailty regression.[10] Similar to what we have reported previously in our baseline cross-sectional analysis of the cohort,[4] none of the biomarkers of inflammation (hs-CRP, IL-6) coagulation (D-dimer), intestinal microbial translocation (I-FABP), and immune activation (sCD14, sCD163) were associated with the odds of transitioning to frailty when added to the multivariable model, nor modified its association with HIV-positive status. This observation is in line with a recent review describing 4 longitudinal studies in HIV-negative populations, in which higher levels of CRP and IL-6 were likewise not associated with transitioning to frailty.[22] However, the inflammatory markers D-dimer, I-FABP, and hsCRP lost significance in multivariable models after adjustment for the number of prevalent comorbidities. Some cross-sectional studies have found inflammatory markers to be associated with frailty in multivariable analysis, supporting the idea that the lack of association found in our study could be explained by those markers being on the same

mechanistic pathway by which increased comorbidities and other factors contribute to frailty.[23–26]

Strengths and Limitations

The strengths of our study include the longitudinal prospective design, the extensive and standardized data collection, and the highly comparable HIV-negative control group. This allowed us to robustly investigate the association between HIV-infection and frailty phenotype transitions, and study a wide set of possible mediators and confounders.

Our study also has some limitations. Because most of our participants had been diagnosed with HIV many years ago, and many had experienced severe immunosuppression or AIDS, these results may not be generalizable to individuals more recently diagnosed with HIV at an earlier stage of infection and immediately treated with contemporary ART regimens. In addition, our cohort consists mainly of white MSM, which limits generalizability. Previous studies found that persons of non-white ethnicity and women may be more prone to become frail.[2,17] Non-MSM men, women, and people with different ethnic backgrounds were underrepresented in our study, which precludes us from examining these potential associations. Inflammatory markers of hepatitis, cytomegalovirus, I-FABP, sCD14, and sCD163 were only measured at enrolment and therefore, the time between these markers and the frailty assessment could be as long as 4 years. The study also lacked complete data on hospitalization, a possible factor associated with transitioning to frailty. Finally, the overall low proportion of participants that became and remained frail limited our ability to examine factors associated with frailty transitioning in greater depth.

CONCLUSIONS

As our study shows, frailty is one end of the spectrum of what is a highly transitional phenotype. Multiple distinct factors may contribute to frailty transitions, with many of those factors —such as higher waist-to-hip-ratio, a higher number of prevalent comorbidities and having depressive symptoms—being potentially preventable and reversible, and thus deserving attention as part of routine HIV care. A recent systematic review showed that increasing the level of physical activity significantly reduced frailty.[27] A growing body of evidence suggests that PWH experience frailty to a greater degree than the general population, and that frailty is associated with adverse outcomes in this population. We advocate that interventions to reduce frailty development should be investigated among our aging HIV patients. Whether increasing the level of physical activity may also prevent transition to frailty and ameliorate its downstream adverse health outcomes, should be investigated among PWH.

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