Frailty is associated with mortality and incident comorbidity among middle-aged HIV-positive and HIV-negative participants.

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SUMMARY

Frailty was a strong predictor of mortality and incident comorbidity in our HIV-positive and HIV-negative population which, whilst ageing, were not yet considered of geriatric age. Moreover, frailty impacted the risk of these outcomes independently from other recognized risk factors.

FOOTNOTES

Conflicts of interests

PR through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co and ViiV Healthcare, and has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, Merck & Co, Teva pharmaceutical industries, for which honoraria were all paid to his institution. GDK was supported by a Fulbright Global Scholar award (US Department of State) and by the National Institute of Allergy and Infectious Diseases (grant number K24-AI118591). FWW has served on scientific advisory boards for ViiV and Gilead sciences. RAVZ has received travel grants from Gilead Sciences, and was a speaker at an event sponsored by Gilead Sciences for which her institution received remuneration. MFSVDL has received independent scientific grant support

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ABSTRACT

Background. Frailty is associated with mortality and morbidity in the general geriatric population, but less is known about its impact among the ageing but generally younger population with HIV (PWH).

Methods. The impact of frailty on all-cause mortality, during 6 years of follow-up and incident comorbidity, during 4 years of follow-up was assessed among 598 HIV-positive and 550 comparable HIV-negative participants of the AGE$_h$IV Cohort Study, aged ≥45 years. Frailty encompasses 5 domains; weight loss, low physical activity, exhaustion, decreased grip strength, and slow gait speed. Presence of ≥3 denotes frailty, 1-2 prefrailty and 0 robust. Multivariable Cox and logistic regression models were used to assess the independent relationships of frailty with both outcomes, adjusting for HIV-infection and traditional risk factors.

Results. At baseline 7.5% (n=86) of participants were frail. During follow-up 38 participants died. Mortality rate was significantly higher among frail participants (frail 25.7/1,000person-years of follow-up (PYFU; 95%confidence interval[95%CI] 14.2-46.4); prefrail 7.2/1,000PYFU (95%CI,4.7-11.2); robust 2.3/1,000PYFU (95%CI,1.1-4.9)). In fully adjusted analyses, frailty remained strongly associated with death (HR4.6,1.7–12.5) and incident comorbidity (OR1.9,1.1–3.1). No interactions were observed between frailty- and HIV-status in all analyses.

Conclusions. Frailty is a strong predictor of both mortality and incident comorbidity independent from other risk factors.

Keywords. “Frailty“; “Mortality“; “Comorbidities“; “HIV”; “Inflammation“

BACKGROUND

With the use of combination antiretroviral therapy (cART), the life expectancy of people living with HIV (PWH) has notably improved,[1] and non-AIDS-defining comorbidities have thereby gained increased importance as causes of morbidity and mortality.[2] Consequently, identifying PWH at increased risk of poor outcomes as they age has become a research priority with important implications for clinical management.

The Frailty Phenotype (frailty), described by Fried was developed in the general population aged ≥65 years to predict morbidity and mortality.[3] Frailty is conceptualized as a state of decreased physical resilience due to deficits across multiple organ systems, leading to increased vulnerability and adverse outcomes such as falls, hospitalisation, disability and death in the general geriatric population.[3, 4] HIV-infection and related chronic systemic inflammation are hypothesized to increase vulnerability to stressors and potentially mediate the association between frailty and adverse health outcomes.[5, 6] Frailty is not synonymous with comorbidities, although there is a bidirectional relationship between frailty and comorbidity whereby frailty can be both a predictor and an outcome of comorbidities.[3, 4, 7, 8]

Frailty has also been shown to be present among younger HIV-positive[5, 9] and -negative individuals.[10] Moreover, previous analyses from our cohort demonstrated that middle-aged (≥45 years) PWH were more likely to be frail[11] and to have a higher comorbidity burden than lifestyle-comparable HIV-negative participants.[12] Few studies prospectively reported on the development of adverse health outcomes in relation to frailty in younger PWH,[10, 13, 14] often not including an appropriately selected HIV-negative comparison group. [14]

As PWH are disproportionally affected by non-HIV-related comorbidities as they age, evaluating the extent to which frailty is predictive of adverse health outcomes could assist in identifying - at an early stage - those at increased risk. We report on the association between frailty-status and the development of mortality and comorbidity among HIV-positive and highly comparable HIV-negative participants of the AGE$_h$IV Cohort Study.

METHODS

Study population

The AGE$_h$IV Cohort Study included 598 HIV-positive participants from the Academic Medical Center 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. [15] As described previously, [12] all participants were ≥45 years of age at enrolment. HIV-negative participants were a highly comparable control group regarding geographic, sociodemographic characteristics and sexual behavior. The majority of HIV-negative participants were men who have sex with men (MSM) at increased risk for HIV infection. Data prospectively collected between October 2010 and October 2018, encompassing four biennial study-visits, were included in the current analysis.

Written informed consent was obtained from all participants. The study protocol was approved by the Academic Medical Center ethics review board and was registered at www.ClinicalTrials.gov (NCT01466582).

Data collection

During each study-visit, standardized measurements of hip and waist circumference, waist-to-hip ratio, height, and weight were performed and blood samples were collected. A standardized

questionnaire collected data on smoking behavior, alcohol use, medication use, recreational drug use, and depressive symptoms, defined as a score of ≥16 on the Center for Epidemiologic Studies Depression questionnaire (CES-D)[16] excluding two questions which were also used in the frailty score, as done previously.[11] Data only collected at baseline were: hepatitis B/C virus serology, Cytomegalovirus 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.

Definitions of comorbidities

Comorbidities objectively assessed during each study-visit were: (1) chronic obstructive pulmonary disease (COPD) (FEV_1/FVC-ratio z-score <-1.64 using Global Lung Initiative guidelines)[17]; (2) hypertension grade 2 (measured systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg in 3 measurements with a 1-minute interval, following European Guidelines[18] or use of antihypertensive medication); (3) decreased kidney function (eGFR <60 mL/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration[CKD-EPI] equation) [19]); (4) osteoporosis (Dual-energy X-ray absorptiometry[DXA] T-score <-2.5 standard deviation for men aged ≥50 years and post-menopausal women or a Z-score <-2.0 for men aged <50 years and pre-menopausal women using World Health Organization definitions)[20]; (5) diabetes mellitus (HbA1c ≥48 mmol/mol or elevated blood glucose (non-fasting ≥11.1 mmol/L or fasting ≥7.0 mmol/L) or using anti-diabetic medication)[21]. Self-reported, but subsequently validated comorbidities included: (6) heart failure (diagnosed by cardiologist); (7) non-AIDSdefining cancers (confirmed by pathologist, excluding non-melanoma skin cancers); and (8) atherosclerotic diseases (diagnosed by specialist; myocardial infarction, angina pectoris, peripheral arterial disease, ischemic stroke or transient ischemic attack). Self-

reported diagnoses were validated using hospital records for HIV-positive participants, and general practitioners'(GP) records for HIV-negative participants who provided consent to contact their GP. For participants who died during follow-up, information on comorbidities and cause of death was obtained using hospital and GP records. Unvalidated diagnoses were used when validation was not possible (i.e., participants not providing consent, or absence of clinical documentation when care received in other hospitals). Of the 262 self-reported comorbidities, 146 (55.7%) were validated as correct, 93 (35.5%) were rejected, and 23 (8.8%) could not be validated. Rejected self-reported comorbidities were excluded from analyses. Incident comorbidities were defined as those which were not present during previous study-visits.

Mortality data were confirmed through the Municipal Personal Records Database, even if participants were lost to follow-up or declined participation in follow-up study-visits. Mortality data were missing only for 15 participants (1.3%) who relocated abroad during follow-up.

Frailty definition

Frailty based on the Fried Frailty Phenotype was assessed at each study-visit,[11] including five dichotomous items, each scored as absent (0) or present (1):(1) self-reported unintentional weight loss (≥ 4.5 kg in the last year or > 2.3 kg in the last six months),(2) self-reported low physical activity,(3) self-reported exhaustion,(4) slow walking speed (4.57 meter walk), and (5) low grip strength (Jamar Plus+ Digital Hand Dynamometer; Jamar; USA). The summary score of this 5-item scale classifies an individual as robust (0 points), prefrail (1-2 points) or frail (3-5 points). In line with current practice,[22] but in contrast to our previous analysis,[11] we used the highest measured grip strength (of 3 measurements) and the highest walking speed (of 2 measurements). If frailty items were missing, we assumed these items to be normal (having a score of 0); 90 visits from HIV-positive and 12 visits from HIV-negative participants were missing one frailty item

(<0.7% of all visits), 7 visits from HIV-positive participants were missing 2 frailty items. We considered the overall frailty score as missing if ≥two frailty items were missing (n=14[<0.5%] among 3,022 study-visits). Data from two participants were excluded because of missing frailty scores at all study-visits.

Statistical analysis

Baseline characteristics were compared between groups using Wilcoxon rank-sum test, ANOVA, and chi-squared tests as appropriate.

All-cause mortality by baseline frailty-status was analyzed using Kaplan-Meier curves and Cox proportional hazards models. For all models with mortality as outcome, follow-up time was censored at the date of death, the fourth study-visit (six years of follow-up), withdrawal of consent, or at the first missed study-visit for those who were lost to follow-up or not attending two consecutive study-visits. We used a stepwise forward selection procedure to identify variables potentially influencing the association of frailty with mortality: all variables with a main effect P-value <0.2 in univariable analyses were retained in the multivariable model if they changed the frailty regression coefficients by at least 10%, or if they remained independently associated with the outcome. Variables explored for their confounding or mediating effects were: age; a composite of gender and sexual behavior (i.e., MSM male, heterosexual male, and female; hereafter called 'sexual risk group'); body composition (body-mass index, waist circumference, hip circumference, and waist-to-hip ratio); smoking (never, ever or current) ; alcohol use (never, ever or current); recreational drug use; number of pre-existing comorbidities (0, 1, 2 or ≥3); depressive symptoms, defined as a CES-D score of ≥16 (Yes/No); chronic hepatitis B or C virus infection; CMV seropositivity; high sensitivity C-reactive protein (hs-CRP), D-dimer and the previously mentioned biomarkers of intestinal permeability, inflammation and immune activation. To

investigate whether the frailty phenotype has different predictive properties in HIV-positive compared to HIV-negative participants, HIV-status and an interaction term between HIV-status and frailty-status was added to the models.

Incident comorbidities were defined as comorbidities newly diagnosed after the first but before or at the second of a pair of consecutive study-visits. If a specific comorbidity known to be chronic (e.g., hypertension) was present during a particular study-visit, we considered it to be present during all subsequent study-visits. Data collected from the initial three study-visits (four years of follow-up) were used, as validation of self-reported comorbidities had not yet been completed for the fourth study-visit. All participants who contributed one or more consecutive visit-pairs (i.e., visit v_1 to v_2 or v_2 to v_3) were included. As frailty tends to be more transitional in younger populations,[23] we chose to only include consecutive visit-pairs, and not non-consecutive visit-pairs (i.e., visit v_1 to v_3). To assess potential selection bias, characteristics of participants at time of enrolment included in this analysis were compared with those who were excluded. Frailty-status as predictor of incident comorbidity was analyzed using logistic regression models with generalized estimating equations using an exchangeable working correlation matrix to account for the clustered observations within an individual. Frailty-status was assessed as a time-updated variable in this model. In the incident comorbidity model, number of pre-existing comorbidities, sexual risk group, non-white ethnicity and level of education were forced into the model based on a priori knowledge. Furthermore, all potential confounding or mediating factors listed under the mortality analyses were also analyzed in the incident comorbidity analysis.

Finally, mediating properties of several HIV-related factors between frailty and both outcomes were investigated among HIV-positive participants only. HIV-related factors explored were: current CD4 cell count, CD4 cell nadir (per 100 cells), CD4/CD8 ratio at time of the study-visit,

level and duration of HIV viraemia (time spent above 1,000/5,000/10,000/75,000/200,000 copies/mL), level and duration of immunosuppression (time spent with a CD4 cell count below 50/100/200/350 cells/uL), having been diagnosed with a CDC-C class AIDS defining event, type of first AIDS defining illness, type and duration of prior ART use, and time since HIV diagnosis. Moreover, we assessed whether hip- or waist-circumference, and the waist-to-hip ratio as possible proxy for lipodystrophy, were associated with both outcomes or attenuated the effect of frailty on both outcomes. Missing categorical or dichotomized variables from all participants were not imputed but categorized as 'missing' and thus included in the model. Missing continuous variables were imputed using mean values stratified by HIV-status and risk group. The amount of missing data was very limited: 0.6% of continuous and 2.3% of categorical variables.

All reported P-values are two-tailed. Interaction effects between covariates were explored in all final models and retained when $P \leq 0.1$. Analyses were performed using Stata version 12 (StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics of study participants at time of enrolment, by frailty-status, are shown in Table1. Stratified by frailty-status, the age distribution was not significantly different between the HIV-positive and HIV negative participants. During follow-up, 35 (7.9% of 441 non-frail) HIV-positive and 25 (5.4% of 466 non-frail) HIV-negative participants became frail. Additionally, 103 (56.9% of 181 robust) HIV-positive and 144 (49.3% of 292 robust) HIV-negative participants became prefrail. The majority of the participants were MSM and of white ethnicity. Frail participants tended to more frequently be HIV-positive, older, a current smoker, and to have more pre-existing comorbidities. However, they reported less alcohol use. Levels of hsCRP, D-dimer, sCD163 and I-FABP were higher among frail participants. The majority of the HIV-positive participants used cART (95.8%) of whom 95.1% were virologically suppressed (defined as HIV RNA <200 copies/mL) in the year prior to enrolment. Median time since HIV-1 diagnosis was 12.0 years (Table2). During follow-up, 7 HIV-negative participants seroconverted, after which they contributed as HIV-positive participants in the analyses.

Mortality

During a median of 4.0 (interquartile range, 2.1-5.9) years of observation, 38 (3.3%) of 1146 participants died, including 31 (5.2%) HIV-positive, and 7 (1.3%) HIV-negative participants. Of the 38 deaths, 11 (29%) were frail at study enrolment, 20 (53%) prefrail and 7 (18%) robust. None of the deaths were AIDS-related. For causes of death see Supplementary Table1.

The mortality analysis included 428, 2771, and 3000 person-years of follow-up (PYFU) for participants who were frail, prefrail and robust at enrolment, respectively. Mortality rates/1,000 PYFU were notably higher among those who were frail 25.7(95%CI,14.2-46.4) compared to those

who were either prefrail (7.2 (95%CI,4.7-11.2) or robust (2.3 (95%CI,1.1-4.9), p<0.001 for both comparisons). See Figure1 for the corresponding Kaplan-Meier cumulative mortality curve.

In stepwise proportional hazards models, the frail phenotype remained independently associated with an increased risk of mortality after stepwise adjustment for age, HIV-status, smoking-status, alcohol use and sCD163 plasma concentration (Table3). The effect of the independent variables included in the final model (Model 6), is shown in Supplementary Table2. All other variables were not associated with mortality nor influenced the effect of frailty on mortality, and were therefore excluded from the final models. There was no interaction effect of HIV and frailty on mortality. Within the HIV-positive group only, after additional adjustment for nadir CD4 count, frailty remained independently associated with mortality (Table4 and Supplementary Table3). Other HIV-related variables, including hip- or waist-circumference, and the waist-to-hip ratio as potential proxy for lipodystrophy were not independently associated with mortality, nor did they attenuate the association between frailty and mortality.

Incident comorbidity

Comorbidity data were available for 497 HIV-positive and 479 HIV-negative participants, including 1833 visit-pairs, in which 107 (5.8%), 788 (43.0%) and, 938 (51.2%) participants were classified as frail, prefrail or robust at the first of the paired study-visits, respectively. There were 33 (30.8%), 160 (20.3%), and 127 (13.5%) incident comorbidities within the frail, prefrail and robust visit-pairs, respectively. Hypertension grade 2 (n=87), COPD (n=69), decreased kidney function (n=41) and osteoporosis (n=39) comprised 74% of all incident comorbidities (n=320 in total).

In unadjusted analyses, being frail or prefrail were each associated with an increased risk of incident comorbidity compared to being robust (OR 2.59 P<0.001, OR 1.60 P=0.003, Table5). For both frailty and prefrailty, the association was attenuated by age (model 2) and HIV-status (model 3), but remained statistically significant. No further attenuation of these associations was observed after inclusion of the number of pre-existing comorbidities, sexual risk group, non-white ethnicity and level of education to the model. No significant interactions were found between variables included in the final model (Table 4 and Table 5, Model 5), including for HIV- and frailty-status.

Within the HIV-positive group, frailty, but not prefrailty, was crudely associated with incident comorbidity (OR 2.34, P=0.002, Supplementary Table 4). Adding age and number of pre-existing comorbidities to the model slightly attenuated the association between frailty and incident comorbidity. Further addition of sexual risk group, level of education and non-white ethnicity to the model did attenuate the association; frailty remained significantly associated with a 2-fold higher risk for incident comorbidity (OR 1.92, P=0.027). While the cumulative duration of zalcitabine use and cumulative exposure to a detectable HIV-viral load were each independently associated with incident comorbidity, the addition of these variables to the model did not substantively impact the association between frailty and incident comorbidity. Other HIV- and ART-related variables, including hip- or waist-circumference, and the waist-to-hip ratio were not associated with incident comorbidity nor did they influence the association between frailty and comorbidity development.

DISCUSSION

We found that in comparable populations of middle-aged HIV-positive and -negative participants, the frailty phenotype was strongly and consistently associated with increased risk for both all-cause mortality and incident comorbidity. Both effects were independent of other traditional risk

factors such as age and smoking behavior. Those who were prefrail were at intermediate risk for both outcomes. These data further contribute to the growing evidence base for the utility of a frailty phenotype for predicting adverse clinical outcomes in ageing but generally younger HIV-positive populations, even among those whom have maintained excellent control of their HIV disease for prolonged periods of time.

Although frailty prevalence was relatively low and we observed few deaths, frailty was strongly predictive of mortality. Similarly observations have been reported from a middle-aged cohort of HIV-positive and negative injection drug users, albeit they had notably higher levels of frailty and mortality with poorer levels of virologic control. [5] Due to the limited number of deaths we observed, potential drivers of this effect could not be extensively investigated. While the association of frailty with mortality was notably attenuated by age, other traditional risk factors (e.g, behavioral factors such as tobacco and alcohol use), HIV-related factors (e.g., CD4 nadir, viral suppression, prior AIDS), or immune activation and inflammation markers had minimal impact on the observed risk and do not explain the association of frailty with mortality. While current smoking was strongly associated with mortality, we interestingly found that current alcohol use was notably less common among frail individuals and was inversely associated with mortality, suggesting that unhealthy participants had likely reduced or stopped their alcohol consumption. Among our virologically controlled HIV-positive participants, most markers of HIV disease stage or a panel of immune activation and chronic inflammation biomarkers were not significantly associated with mortality. CD4 nadir, a previously reported risk factor for mortality, [24] was associated with a 50% reduced survival per 100 cell decrease. sCD163, similar to a report by Knudsen et al., [25] was the only measured marker associated with mortality in our analysis. However, neither CD4 nadir nor sCD163 attenuated the association between frailty and mortality.

The interaction between HIV- and frailty-status was deemed nonsignificant, which suggests equivalent predictive ability of frailty for mortality in virologically controlled HIV-positive patients and lifestyle-comparable HIV-negative persons. This conclusion should however be taken with caution as the number of deaths among the HIV-negative participants was only 7.

Frailty was also associated with a higher risk of developing one or more comorbidities. This association was independent of the number of prevalent comorbidities at enrolment and of other traditional risk factors such as age, tobacco and alcohol use. A recent study among PWH has shown frailty to be predictive of bone disease, diabetes, and cardiovascular disease. [26] To our knowledge, we are the first to report the predictive value of frailty on a composite of age-associated comorbidities in PWH. This is especially relevant for our ageing PWH population, which is at increased risk for a wide variety of comorbidities spanning multiple organ systems. Fried describes frailty as a "physiologic precursor and etiologic factor of disability", but not as being synonymous with comorbidity or disability. [3] We show that frailty indeed predicts comorbidity development independently from pre-existing diagnosed comorbidities or other risk factors. Although several HIV-related variables (duration of zalcitabine use and the cumulative duration of a detectable viral load) and HIV-status itself were associated with incident comorbidity, frailty remained independently associated with incident comorbidities in PWH. Although hypothesized to drive comorbidity risk in PWH, markers of chronic inflammation,[27, 28] immune activation[29] and microbial translocation[30] did not influence the association between frailty and incident comorbidity. These findings suggest a distinct independent pathophysiological pathway, not captured by factors measured in our study.

Strengths and limitations

Our study has several practical limitations. We observed few deaths, so we had limited statistical power to analyze factors associated with mortality. Markers of inflammation and immune activation (IL-6, sCD14, sCD163 and I-FABP) were only measured at enrolment. For the analysis of comorbidity development, follow-up time was limited to 4 years. As the majority of our participants had been diagnosed with HIV for a long time, and many had experienced severe immunosuppression or AIDS, these results may not be generalizable to individuals who are more recently diagnosed with HIV and immediately treated with contemporary ART regimens. Additionally, we were unable to analyze the impact of frailty on both outcomes in HIV-negative participants only, as the number of frail HIV-negative participants was low, and the number of outcomes even lower.

The strengths of our study are the longitudinal prospective design, the extensive and standardized data collection, and the highly comparable HIV-negative control group. This allowed us to investigate the association between frailty and mortality and incident comorbidity in both HIV-positive and negative participants, controlling for a wide set of possible mediators and confounders. Additionally, the majority of self-reported diagnoses could be validated by review of medical charts, and other comorbidities were based on objective clinical, physiologic or laboratory data.

Conclusion

Frailty was a strong predictor of mortality and incident comorbidity in this predominantly middle-aged HIV-positive population which, whilst ageing, would not yet be considered of geriatric age. Moreover, frailty impacted the risk of these adverse outcomes independently from other

recognized risk factors. PWH are known to develop frailty and age-associated comorbidities both more frequently and at a younger age. Implementing a frailty assessment in HIV-care and clinical trials could therefore be useful for improving risk stratification, clinical management and preventing adverse health outcomes in this high risk population. Furthermore, evidence suggests that once identified as being frail, sustained physical activity may improve the frailty score among elderly persons[31]. Future studies should investigate if such interventions may similarly modify the frailty-phenotype in ageing PWH to reduce their risk of morbidity and mortality.

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TABLE 1: Baseline characteristics of participants included in the AGEhIV Cohort stratified by frailty status

	Robust (n=547)	Prefrail (n=513)	Frail (n=86)	
	n (%), median (IQR), or mean (SD)	n (%), median (IQR), or mean (SD)	n (%), median (IQR), or mean (SD)	p-value
Demographics				
HIV-positive	214 (39.1%)	313 (61.0%)	69 (80.2%)	<0.001[+]
HIV-negative	333 (60.9%)	200 (39.0%)	19 (19.8%)	
Age, years	51.5 (47.6, 56.9)	53.3 (48.6, 60.1)	55.1 (49.7, 60.0)	<0.001[++]
Sexual risk group				
MSM male	399 (72.9%)	378 (73.7%)	61 (70.9%)	0.29[+]
Non-MSM male	79 (14.4%)	62 (12.1%)	8 (9.3%)	
Female	69 (12.6%)	73 (14.2%)	17 (19.8%)	
Non-white ethnicity	39 (7.1%)	46 (9.0%)	12 (14.1%)	0.085[+]
White ethnicity	508 (92.9%)	467 (91.0%)	74 (86%)	
Higher-education[1]	276 (50.5%)	211 (41.1%)	22 (25.6%)	<0.001[+]
Behavioral characteristics				
Smoking status				
Never	198 (37.8%)	152 (31.6%)	21 (27.3%)	0.023[+]
Former	194 (37.0%)	170 (35.3%)	27 (35.1%)	
Current	132 (25.2%)	159 (33.1%)	29 (37.7%)	

Pack-years (if ever smoked)	15.0 (3.4, 31.5)	18.7 (8.1, 35.0)	22.8 (7.0, 39.0)	<0.001[++]
Alcohol use				
Never	31 (5.9%)	27 (5.5%)	12 (15.4%)	<0.001[+]
Former	43 (8.1%)	63 (12.8%)	12 (15.4%)	
Current	454 (86.0%)	401 (81.7%)	54 (69.2%)	
Heavy-daily alcohol use past 6 months[2]	28 (5.1%)	24 (4.7%)	2 (2.3%)	0.009[+]
Binge alcohol during past 6 months[3]	147 (26.9%)	112 (21.8%)	12 (14.0%)	0.006[+]
Injection drug use (ever)	8 (1.5%)	11 (2.1%)	6 (7.0%)	<0.001[+]
THC use during last 6 months	53 (10.3%)	68 (14.6%)	8 (11.0%)	0.120[+]
Body composition				
Waist-circumference, cm	91.9 (9.9)	93.2 (11.1)	95.5 (11.7)	0.005[+++]
Waist-to-hip ratio	0.9 (0.1)	1.0 (0.1)	1.0 (0.1)	<0.001[+++]
Body-mass-index, kg/m²	25.0 (3.3)	24.9 (3.8)	25.4 (4.6)	0.48[+++]
Comorbidity				
Number of age-associated comorbidities				
0	334 (61.1%)	264 (51.5%)	37 (43.0%)	<0.001[+]
1	152 (27.8%)	162 (31.6%)	23 (26.7%)	
2	47 (8.6%)	58 (11.3%)	17 (19.8%)	
≥3	14 (2.6%)	29 (5.7%)	9 (10.5%)	

Hepatitis B virus DNA positive	12 (2.2%)	25 (4.9%)	4 (4.7%)	0.052[+]
Hepatitis C virus RNA positive	5 (0.9%)	15 (2.9%)	7 (8.2%)	<0.001[+]
Cytomegalovirus IgG positive	450 (82.3%)	449 (87.9%)	78 (90.7%)	0.013[+]
Depressive symptoms[5]				
CES-D ≥16	41 (7.5%)	101 (19.7%)	36 (41.9%)	<0.001[+]
Markers of inflammation				
hsCRP, mg/L	1.0 (0.6, 2.0)	1.5 (0.7, 3.1)	1.8 (0.7, 3.9)	<0.001[++]
D-dimer, mg/L	0.2 (0.2, 0.3)	0.3 (0.2, 0.4)	0.3 (0.2, 0.5)	0.009[++]
IL-6, pg/mL	1.8 (1.1, 3.1)	1.7 (1.1, 2.8)	1.8 (1.1, 3.8)	0.54[++]
sCD14, ng/mL	1472 (1166, 1872)	1496 (1229, 1935)	1423 (1148, 1873)	0.15[++]
sCD163, ng/mL	260 (189, 352)	279 (190, 379)	320 (244, 495)	<0.001[++]
I-FABP, ng/mL	1.4 (0.9, 2.2)	1.8 (1.1, 3.0)	2.0 (1.4, 3.3)	<0.001[++]

[1]Higher vocational education; attained at least a bachelor's degree

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

[3]Binge alcohol defined as >6 alcohol units a day, minimally once per month during the last 6 months

[4]Comorbidities included are chronic obstructive pulmonary disease or asthma (defining obstruction as having lower than 1.64 z-score for FEV1/FVC-ratio using Global Lung Initiative guidelines), diabetes (HbA1c ≥ 48 mmol/mol and/or elevated blood glucose (non-fasting ≥ 11.1 mmol/L or fasting ≥ 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 mmHg and/or diastolic blood pressure 100 mmHg in all 3 measurements), decreased kidney function (eGFR <60 mL/min/1.73 m^2) 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 ≥50 years and postmenopausal women), self-reported and validated heart-failure, non-AIDS associated cancer (excluding non-melanoma skin cancers), cardiovascular disease (myocardial infarction, angina pectoris, peripheral artery disease, ischemic stroke and/or transient ischemic attack).

[5]CES-D scale ≥ 16, with two questions used in the frailty scale excluded from CES-D score calculation.

[+] Pearson's chi-squared test

[++] Kruskal – Wallis test

[+++] ANOVA

Abbreviations: IQR, interquartile range; SD, standard deviation, MSM, men who have sex with men; THC, Tetrahydrocannabinol; CES-D, Center for Epidemiologic Studies Depression scale; hsCRP, high sensitive C-reactive protein; IL-6, interleukin -6. sCD14, soluble CD14; sCD163, soluble CD163; I-FABP, intestinal fatty acid-binding protein

TABLE 2: Characteristics of HIV-positive participants

	(N = 596)
	n (%) or median (IQR)
Years since HIV-diagnosis	12.0 (6.6. 17.1)
CD4 cell count, cells/µL	
Nadir CD4 count	170 (70 - 260)
Mean CD4 in 12 months prior to enrolment	565 (432 - 740)
Cumulative duration of CD4 count <200/µL (years)	0.9 (0.0 - 10.5)
CD4/CD8 ratio at enrolment	0.7 (0.5 - 1.0)
History of CDC-C class AIDS defining diagnosis	192 (32.2%)
Using cART at enrolment	571 (95.8%)
Cumulative exposure to ART, years	10.3 (4.5 - 14.5)
ART-experienced before starting cART	120 (21.0%)
Having used zalcitabine	169 (28.4%)
Duration of zalcitabine use (years)[1]	2.7 (0.9 – 6.9)
HIV-RNA <200 c/mL in year prior to enrolment[2]	542 (95.1%)
cumulative duration of HIV-RNA <200c/mL, years[2]	8.7 (3.9-12.6)

[1] for those who had used zalcitabine

[2] if currently on cART

Abbreviations: IQR, interquartile range; ART, antiretroviral therapy; cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention

FIGURE 1: Kaplan-Meier cumulative mortality curve for the 1,146 participants of the AGE$_h$IV Cohort for all-cause mortality by frailty status at enrolment from October 2010 until October 2018.

Follow-up time was censored at date of death, the fourth study-visit, withdrawal of consent, loss to follow-up, or 6 years after inclusion for participants who did not complete their fourth study-visit. Participants who missed two consecutive study-visits were considered lost to follow-up and were censored at time of the first missed study-visit. Frailty was defined based on the presence of ≥3 criteria, 'prefrail' if 1-2 criteria were present, and 'robust' when none of the criteria were met. The number of participants at risk are noted in the table below the graph.

TABLE 3: Association between frailty status at enrolment and subsequent mortality; results of a Proportional Hazards model analysis

	Hazards ratios (95%CI) of frailty phenotype compared to robust phenotype	
	Prefrail	Frail
Model 1	3.08 (1.30- 7.28)	10.87 (4.21 – 28.07)
	P=0.10	P<0.001
Model 2	2.68 (1.12 - 6.40)	8.87 (3.38 – 23.28)
	P=0.026	P<0.001
Model 3	2.25 (0.93 - 5.39)	6.21 (2.31- 16.73)
	P=0.071	P<0.001
Model 4	1.96 (0.81– 4.69)	5.84 (2.21 – 15.46)
	0.133	P<0.001
Model 5	1.85 (0.77 – 4.47)	5.26 (1.97 – 14.05)
	0.172	P=0.001
Model 6	1.86 (0.77 – 4.49)	4.64 (1.72 – 12.50)
	0.165	P=0.002

Model 1: unadjusted

Model 2: adjusted for age

Model 3: further adjusted for HIV

Model 4: further adjusted for smoking-status

Model 5: further adjusted for alcohol-status

Model 6: further adjusted for log-transformed sCD163 plasma concentration

Abbreviations: CI, confidence interval; P, p-value

TABLE 4: Final multivariable models showing the association of independent variables on mortality (Supplemental Table 3, Model 5) and on incident comorbidity (Supplemental Table 4, Model 6), among HIV-positive participants only

Dependent variable	Outcome mortality HR (95% CI)	p-value	Outcome incident comorbidity OR (95% CI)	p-value
Frailty phenotype				
Robust	ref		ref	
Prefrail	1.96 (0.71- 5.39)	0.192	1.08 (0.74- 1.57)	0.678
Frail	3.19 (1.02-9.98)	0.047	1.90 (1.06 – 3.41)	0.032
Age (per 10 years)	1.94 (1.23-3.07)	0.005	1.53 (1.20 – 1.96)	0.001
Sexual risk group				
MSM-male	-	-	ref	
Non-MSM-male	-	-	0.90 (0.50 – 1.63)	0.731
Female	-	-	1.84 (1.08 – 3.12)	0.024

Non-white ethnicity	-	-	1.18 (0.62 – 2.22)	0.617
Higher vocational education	-	-	0.91 (0.63 – 1.31)	0.608
Smoking status				
Never	ref		ref	
Former	1.16 (0.35 – 3.87)	0.804	1.04 (0.67- 1.62)	0.847
Current	3.41 (1.19 – 9.77)	0.022	1.46 (0.93 – 2.27)	0.099
Alcohol use				
Never	ref		ref	
Former	0.27 (0.06 – 1.16)	0.078	0.74 (0.34 – 1.61)	0.451
Current	0.20 (0.05 – 0.77)	0.019	0.69 (0.35 – 1.35)	0.274
Number of pre-existing comorbidities				
0			ref	
1	-		0.85 (0.57 – 1.28)	0.439
2	-		0.87 (0.51 – 1.47)	0.596
≥3	-	-	0.66 (0.34 – 1.27)	0.212
CD4 nadir (per 100 cells/uL higher)	1.51 (1.06 - 2.14)	0.022	-	-
Duration of zalcitabine use (years)	-	-	1.35 (1.09 – 1.67)	0.005
Cumulative duration of viral load > 1000 copies/mL	-	-	1.06 (1.00 – 1.12)	0.046

Abbreviations: HR, hazard ratio; OR, odds ratio; CI, confidence interval

TABLE 5: Association between frailty status and incident comorbidity risk; results of a logistic regression model analysis with generalized estimated equations

	Odds ratios (95%CI) of frailty phenotype compared to robust phenotype	
	Prefrail	Frail
Model 1	1.60 (1.24- 2.08)	2.59 (1.62 – 4.13)
	P=0.003	P<0.001
Model 2	1.46 (1.12-1.92)	2.24 (1.40 – 3.61)
	P=0.005	P=0.001
Model 3	1.38 (1.06 – 1.82)	2.01 (1.24 – 3.26)
	P=0.019	P=0.005
Model 4	1.38 (1.05– 1.82)	2.03 (1.23 – 3.34)
	P=0.020	P=0.005
Model 5	1.34 (1.02 – 1.77)	1.87 (1.13- 3.10)
	P=0.036	P=0.015

Model 1: unadjusted

Model 2: adjusted for age

Model 3: further adjusted for HIV

Model 4: further adjusted for non-white ethnicity, education, risk group and number of pre-existing comorbidities

Model 5: further adjusted for smoking behavior and alcohol use

Abbreviations: CI, confidence interval; P, p-value

Figure 1