

HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls

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Background: Frailty is an age-related syndrome of decreased physiological reserve and resistance to stressors, associated with increased morbidity and mortality in the general elderly population. An increased prevalence of frailty has been reported amongst HIV-infected individuals.

Methods: Frailty phenotype was systematically assessed in predominantly virologically suppressed HIV type 1 (HIV-1)-infected and otherwise comparable HIV-uninfected participants aged at least 45 at enrollment into the AGE_hIV Cohort Study. Multivariable ordinal logistic regression was used to investigate associations between HIV- and antiretroviral therapy-related covariates, markers of inflammation and body composition and prefrailty/frailty.

Results: Data were available for 521 HIV-infected and 513 HIV-uninfected individuals. Prevalence of frailty (10.6 versus 2.7%) and prefrailty (50.7 versus 36.3%) were significantly higher in HIV-infected individuals ($P_{\text{trend}} < 0.001$). HIV infection remained statistically significantly associated with prefrailty/frailty after adjustment for age, sex, race/ethnicity, smoking, hepatitis C infection, comorbidities and depression [adjusted odds ratio (OR_{adj}) 2.16, $P < 0.001$]. A higher waist-to-hip ratio attenuated the coefficient of HIV-infected status (OR_{adj} 1.93, $P < 0.001$), but not waist- or hip-circumference individually or markers of inflammation. Within the HIV-infected group, parameters related to body composition were most strongly and independently associated with prefrailty/frailty: current BMI less than 20 kg/m² (OR 2.83, $P < 0.001$), nadir BMI less than 20 kg/m² (OR 2.51, $P < 0.001$) and waist-to-hip ratio (OR 1.79 per 0.1 higher, $P < 0.001$).

Conclusion: HIV infection was independently associated with prefrailty/frailty in middle-aged HIV-infected patients compared with HIV-uninfected controls. This partly may be mediated by the higher waist- and lower hip-circumference in the HIV-infected individuals, potentially partially caused by lipodystrophy, and in part be a consequence of historic weight loss associated with advanced HIV-disease.

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Introduction

Frailty is a clinical syndrome with multiple causes and contributors, resulting in enhanced vulnerability to stressors and increased risk of adverse outcomes. Several operational definitions are used; the frailty phenotype, operationalized by Fried *et al.* is characterized by unintentional weight loss, diminished gait speed and grip strength, exhaustion and low energy expenditure [1]. The frailty phenotype has been associated with increased mortality and morbidity in the general population [1,2]. Prefrailty, a possibly reversible intermediate state, has also been associated with adverse outcomes, though the risk increase is less pronounced [1].

A higher frailty phenotype prevalence in HIV-infected compared with HIV-uninfected populations has been observed [3–7]. Several studies reported associations between frailty, immunodeficiency [3,4,6,8,9] and AIDS [3,4,7]. Inflammation and immune activation, likely important in the pathophysiology of frailty in the general population [2,10–12], may be mediating the association between HIV infection and frailty [13,14]. Body composition changes, particularly abdominal obesity, may be involved in the pathophysiology of frailty in the general population [15–17]. Both HIV infection by itself as well as exposure to antiretroviral therapy (ART) may contribute to body composition changes, and thereby to the development of frailty in the context of HIV [18].

Within the AGE_{HIV} Cohort Study we systematically assessed the frailty phenotype in HIV type 1 (HIV-1)-infected individuals aged at least 45, and concurrently in HIV-uninfected individuals with a similar demographic and behavioral background. We compared the prevalence of frailty and prefrailty and investigated whether HIV was independently associated with prefrailty and frailty. Additionally we explored the role of comorbidities, markers of inflammation and body composition, and HIV-disease and ART-related factors as possible mediators in the relation between HIV, prefrailty and frailty.

Methods and materials

Study population

Between 2010 and 2012, 597 HIV-1-infected individuals, aged at least 45, were enrolled into the AGE_{HIV} Cohort Study at the HIV outpatient clinic of the Academic Medical Center, Amsterdam, the Netherlands. Five hundred and fifty-one HIV-uninfected individuals, aged at least 45, were recruited from the sexual health clinic and the Amsterdam Cohort Studies on HIV/AIDS at the Amsterdam Public Health Service, as a comparable control group with a similar geographical, socio-demographic and behavioral background. Participants

undergo a biennial standardized screening for age-associated comorbidities and organ dysfunction. Details concerning study procedures have previously been published [19].

Detailed information concerning HIV infection and ART history was obtained from the HIV Monitoring Foundation registry [20].

Written informed consent was obtained from all participants; the study was approved by the local ethics review board (ClinicalTrials.gov identifier NCT01466582).

Definitions

The frailty phenotype, as modified by Önen, was assessed in all participants in a standardized manner [1,21]. Presence of at least three out of five criteria was defined as frailty, presence of 1–2 was defined as prefrailty and absence of all five factors was considered nonfrail. Self-reported unintentional weight loss (1) was considered present if exceeding 4.5 kg in the last year or 2.3 kg in the last 6 months. Low physical activity (2) was considered present if participant answered ‘yes, limited a lot’ when asked whether their health limits vigorous activities such as running, lifting heavy objects, participating in strenuous sports. Exhaustion (3) was present if participant answered “occasionally” or “most of the time” to either one of the following statements: During the last week, how often have you felt that (a) everything you did was an effort, or (b) you could not ‘get going’ [two questions from the Center for Epidemiologic Studies Depression (CES-D) scale]. Maximum grip strength (4) was assessed using Jamar handheld dynamometer (Jamar Plus+ Digital Hand Dynamometer, Jamar, USA), the mean value of three consecutive measurements of the dominant hand was used for analysis. Study participants with pain in the dominant hand, or a missing hand, were excluded from grip strength assessment. Participants were asked to walk a distance of 4.57 m (15 ft) at their own usual pace (5). The average of two consecutive measurements was used. Individuals were excluded from walking speed assessment if walking was painful, if they needed a support device, if they were unable to walk or if one of the legs was missing or incomplete. The cohort, including both HIV-uninfected and HIV-infected individuals, was stratified using the strata as previously described by Fried [1] (Appendix 1, <http://links.lww.com/QAD/A795>). The criteria were considered present in the per stratum lowest quintile. Individuals with one missing criterion were classified as frail, prefrail or missing if respectively at least three, one or zero frailty criteria were present. Individuals with two missing criteria were classified as frail if at least three frailty criteria were present and missing if otherwise.

The number of age-associated noncommunicable comorbidities (AANCC) was categorized in zero, one,

two or at least three comorbidities. Conditions included were hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, osteoporosis, myocardial infarction, angina pectoris, peripheral arterial disease, ischemic cerebrovascular disease and non-AIDS/AIDS associated cancer, according to previously reported criteria [19]. Metabolic syndrome was diagnosed according to the harmonized definition described by Alberti *et al.* [22] (Appendix 2, <http://links.lww.com/QAD/A795>).

Presence of depressive symptoms was assessed using the CES-D scale, excluding two questions that are used in the definition of frailty. Depressive symptoms were stratified in three categories, using both the classical cut-off value for major depression (score ≥ 16) and a more stringent cut-off (score ≥ 25) [23].

Statistical analysis

Statistical analysis was performed using STATA version 12. Characteristics and prevalence of prefrailty and frailty were compared between study groups using χ^2 , Student's *t*, and (Cuzick's extension of) Wilcoxon's rank-sum tests where appropriate. All reported *P*-values are two-sided.

After testing the proportionality of odds across categories nonfrail, prefrail and frail, using a likelihood ratio test, a multivariable ordered logistic regression model was constructed. The independent association between HIV infection and the three frailty categories (nonfrail, prefrail and frail) was investigated. The resulting odds ratio (OR) represents the ratio of the odds for being prefrail compared with nonfrail and for being frail compared with prefrail (the OR for being classified in a higher frailty category). All models were adjusted for age, sex and race/ethnicity. Behavioral factors (heavy alcohol intake, intravenous drug use, and smoking) and the presence of chronic viral hepatitis were explored as potential confounders. The presence of comorbidities, depression, metabolic syndrome, as well as markers of body composition (waist- and hip-circumference, BMI), inflammation and immune activation [high sensitivity C-reactive protein (hsCRP), D-dimer, soluble (s)CD163 and sCD14] were investigated as potentially lying on the causal pathway by analyzing whether their addition to the model attenuated the relation between HIV-status and (pre)-frailty at least 10%. A bidirectional elimination approach was used, the entry criterion being a *P*-value < 0.05 and the exit criterion a *P*-value > 0.1 . Statistical interactions between HIV-status and explored covariates were investigated as well.

HIV- and ART-associated factors were explored in a multivariable model including only HIV-infected individuals.

Results

Frailty assessment was performed in 594 HIV-infected and 550 uninfected individuals. Seventy-three HIV-infected and 29 uninfected individuals were excluded from this analysis, due to missing values for grip strength and walking speed assessment ($n = 24$ and $n = 11$) or incomplete questionnaire data ($n = 49$ and $n = 18$). Individuals with incomplete data were more often women (22.7 vs. 12.8%, $P = 0.004$) and slightly but not significantly younger (51.3 vs. 52.6 years, $P = 0.55$). Individuals without an available questionnaire were borderline significantly more often frail (13.3 vs. 6.7%) and prefrail (45.3 vs. 43.5%), $P_{\text{trend}} = 0.07$.

The 521 HIV-infected and 513 uninfected individuals included in this analysis were comparable regarding age and sex. HIV-infected individuals were more often of black race/ethnicity (12.7 vs. 5.5%, $P < 0.001$), had slightly lower median BMI (24.2 vs. 24.5 kg/m², $P = 0.02$), higher median waist (93.5 vs. 90.7 cm, $P = 0.01$) and lower median hip-circumference (96.6 vs. 99.0 cm, $P < 0.001$) and were more often smokers (32.4 vs. 24.5%, $P = 0.005$). HIV-infected individuals were more often diagnosed with AANCC and more often had depression (Table 1). Median known duration of HIV infection was 12.0 years. About 94.4% of HIV-infected patients were currently on combination (c)ART, of whom 93.3% had undetectable HIV-1 RNA (< 200 c/ml) in the year prior to enrollment (Table 2).

Frailty

HIV-infected individuals were more likely to be frail (10.6 vs. 2.7%) and prefrail (50.7 vs. 36.3%) than HIV-uninfected individuals ($P_{\text{trend}} < 0.001$); this was true for all age-categories (Fig. 1). All five individual frailty criteria were more often present in HIV-infected than in HIV-uninfected individuals (Fig. 2). We observed no significant differences in the distribution of criteria contributing to a prefrail or frail state in HIV-infected compared with uninfected individuals.

In unadjusted ordered logistic regression, the OR for a higher frailty category for HIV-infected status was 2.60 [95% confidence interval (CI) 2.04–3.32, $P < 0.001$]. After adjusting for age, sex, black race/ethnicity, smoking and chronic hepatitis C virus (HCV) (co)infection in multivariable regression, HIV-infected status remained significantly associated with a higher OR ($OR_{\text{adjusted}} 2.39$, 95%CI 1.85–3.09, $P < 0.0001$). Heavy alcohol intake [$\geq 3/\geq 5$ units/day (women/men)], intravenous drug use, and chronic hepatitis B virus (HBV) (co)infection were not significantly associated with a higher OR for frailty and prefrailty nor did they attenuate the OR of HIV-infected status.

The OR of HIV-infected status was slightly attenuated after depression and AANCC were introduced in the

Table 1. Characteristics of HIV-infected and HIV-uninfected participants.

	HIV-infected <i>n</i> = 521 <i>n</i> (%) or median (IQR)	HIV-uninfected <i>n</i> = 513 <i>n</i> (%) or median (IQR)	<i>P</i> ^a
Age (years)	52.8 (48.2–59.5)	52.1 (47.9–58.1)	0.28
45–50	186 (35.7%)	194 (37.8%)	0.42
50–55	127 (24.4%)	130 (25.3%)	
55–60	95 (18.2%)	81 (15.8%)	
60–65	57 (10.9%)	66 (12.9%)	
>65	56 (10.8%)	42 (8.2%)	
Male sex	462 (88.7%)	440 (85.8%)	0.16
MSM	386 (74.8%)	360 (70.7%)	0.14
Black race/ethnicity	66 (12.7%)	28 (5.5%)	<0.001
Smoking			
Current	168 (32.4%)	125 (24.5%)	0.02
Past	181 (34.9%)	198 (38.8%)	
Pack years (ex-) smokers	14.2 (4.5–28.7)	20.7 (7.6–36.4)	<0.001
Heavy ^b alcohol intake in past 6 months	26 (5.0%)	38 (7.4%)	0.11
Intravenous drug use (ever)	18 (3.5%)	6 (1.2%)	0.01
HBV			
Cleared	270 (51.8%)	123 (24.1%)	<0.001
Chronic (HBsAg positive)	33 (6.3%)	3 (0.6%)	<0.001
HCV			
Cleared	31 (6.0%)	3 (0.6%)	<0.001
Chronic (HCV RNA positive)	15 (2.9%)	6 (1.0%)	0.009
Depression ^c	6 (2–13)	4 (1–9)	0.0001
CES-D ≥16	99 (19.5%)	69 (13.5%)	0.01
CES-D ≥25	35 (6.9%)	17 (3.3%)	0.01
Number of AANCC diagnosed			
0	147 (28.2%)	192 (37.4%)	<0.001
1	185 (35.5%)	199 (38.8%)	
2	125 (24.0%)	96 (18.7%)	
≥3	64 (12.3%)	26 (5.1%)	
Metabolic syndrome	171 (33.5%)	137 (28.3%)	0.08
Waist-circumference (cm)	93.5 (86.3–100.5)	90.7 (84.8–97.5)	0.01
Waist-circumference above cut-off ^d	275 (53.0%)	217 (42.6%)	0.001
Hip-circumference (cm)	96.6 (92.0–101.0)	99.0 (95.6–103.2)	<0.001
WHR	0.97 (0.92–1.01)	0.92 (0.87–0.96)	<0.001
WHR above cut-off ^e	436 (83.7%)	321 (62.6%)	<0.001
BMI (kg/m ²)	24.2 (22.3–26.5)	24.5 (22.9–27.0)	0.02
<20	43 (8.3%)	17 (3.3%)	0.006
20–25	267 (51.3%)	279 (54.4%)	
25–30	171 (32.8%)	168 (32.8%)	
≥30	40 (7.7%)	49 (9.6%)	
hsCRP (mg/l)	1.5 (0.7–3.4)	1.0 (0.6–1.9)	<0.001
D-dimer (mg/l)	0.22 (0.20–0.35)	0.24 (0.20–0.38)	0.09
sCD14 (ng/ml)	1589 (1314–2012)	1353 (1074–1738)	<0.001
sCD163 (ng/ml)	289 (207–417)	251 (182–336)	<0.001

AANCC, age-associated noncommunicable comorbidities; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; hsCRP, high sensitivity C reactive protein; sCD14, soluble CD14; sCD163, soluble CD163; WHR, waist-to-hip ratio.

^a*P*-value calculated using Student's *t*-test, χ^2 test, Wilcoxon's rank-sum test where applicable.

^bconsumption of ≥3/≥5 (women/men) alcohol units per day.

^cCenter for Epidemiologic Studies Depression (CES-D) scale, two questions used in frailty scale where excluded from calculation.

^d≥94 cm/≥80 cm (women/men).

^e≥0.85/≥0.9 (women/men).

model (OR_{adjusted} 2.16, 95%CI 1.66–2.83, *P* < 0.001). The metabolic syndrome was not independently associated with a higher frailty category, nor was a waist-circumference above the cut-off or a higher hip-circumference. However, a higher waist-to-hip ratio (WHR) was independently associated with a higher frailty category, and adjustment for the WHR significantly attenuated the OR of HIV-infected status (OR_{adjusted} 1.93, 95%CI 1.46–2.55, *P* < 0.001). After introducing the WHR into the model, the number of AANCC was no longer statistically significantly associated with a higher frailty category, and

therefore excluded from the model. Introduction of BMI attenuated the OR of being HIV-infected further (OR_{adjusted} 1.74, 95%CI 1.31–2.32, *P* < 0.001). A statistically significant interaction was observed between BMI and HIV-status; compared with having a BMI of 20–25, 25–30 or at least 30 kg/m², a BMI less than 20 kg/m² was associated with falling in a higher frailty category in HIV-infected (OR 6.14, 95%CI 3.10–12.18, *P* < 0.001), but not in HIV-uninfected individuals (OR 0.67, 95%CI 0.21–2.19, *P* = 0.51) (*P*_{interaction} = 0.001).

Table 2. HIV and ART-related characteristics of HIV-infected participants.

	HIV-infected <i>n</i> = 521 <i>n</i> (%) / median (IQR)
Years since HIV-1 diagnosis	12.0 (6.1–17.0)
CD4 ⁺ cell count (cells/ μ l)	
Mean value in year prior to enrollment	563 (433–745)
Nadir	180 (78–260)
Cumulative known duration of CD4 ⁺ cell count <200 (months)	0.8 (0–8.5)
History of AIDS	360 (69.5%)
Nadir BMI <20 kg/m ²	118 (22.7%)
Using cART at enrollment	492 (94.4%)
Cumulative duration of exposure to ART, years	9.8 (4.1–14.2)
ART experienced before start of cART	101 (20.5%)
Exposure to dideoxynucleoside analogues, ever/duration (years)	232 (47.2%) / 0 (0–4.44)
Exposure to protease inhibitors, ever/duration (years)	370 (75.2%) / 2.05 (0.01–6.85)
HIV-1 viral load <200 copies/ml in year prior to enrollment (of those on cART)	459 (93.3%)

ART, antiretroviral therapy; cART, combination ART.

sCD14, sCD163, D-dimer and hsCRP were not independently associated with a higher frailty category nor did they attenuate the OR of HIV-infected status significantly.

There were no significant interactions between HIV-infected status and age or any other covariate. The final model is shown in Table 3.

Sensitivity analyses

We repeated the model from Table 3, excluding several subgroups of HIV-infected individuals, to explore whether the observed association between HIV and a higher frailty category was caused by a certain subgroup within the HIV-infected cohort. When those HIV-infected individuals who were ART experienced before start of cART were excluded, HIV-infected status remained significantly associated with a higher frailty category (OR_{adjusted} 1.49, 95%CI 1.10–2.02, $P=0.009$). The relation between WHR and frailty category

remained statistically significant as well (OR 1.54, 95%CI 1.23–1.92, $P<0.001$). Similarly, HIV-infected status remained statistically significantly associated with a higher frailty category when individuals with a history of AIDS, or with a nadir CD4⁺ T-cell count (CD4⁺ cell count) less than 100 cells/ μ l were excluded.

HIV-related determinants of frailty

We explored HIV- and ART-related variables in the multivariable model including only HIV-infected individuals, adjusting for age, sex, black race/ethnicity, HCV coinfection, smoking and depression. The duration of having had a CD4⁺ cell count less than 200 (OR 1.14/year, 95%CI 1.00–1.30, $P=0.04$) as well as the cumulative duration of exposure to protease inhibitors (OR 1.05/year, 95%CI 1.01–1.10, $P=0.01$) were independently associated with a higher OR for a higher frailty category. Exposure to any other type of ART, including dideoxynucleoside analogues (D-drugs), stavudine in particular or mono- and dual ART were not

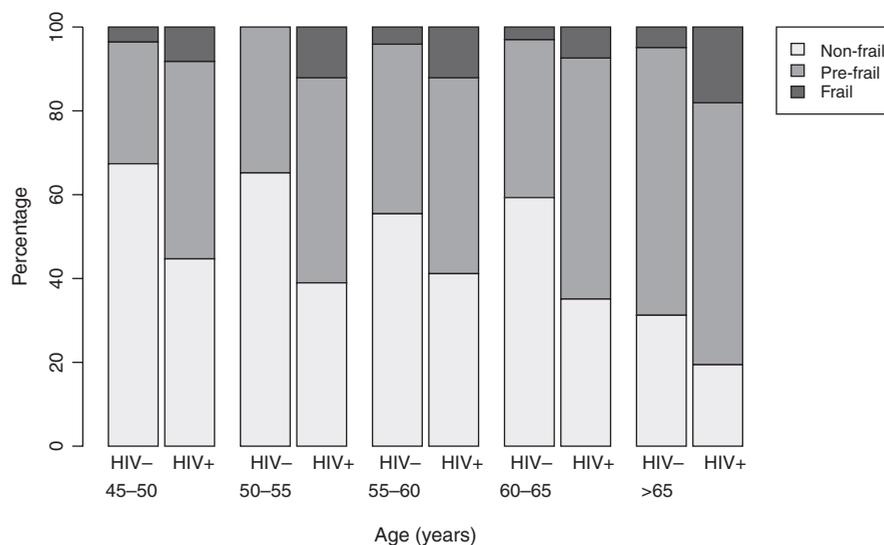


Fig. 1. Prevalence of frailty by age, in HIV-uninfected (HIV-) and HIV-infected (HIV+) individuals.

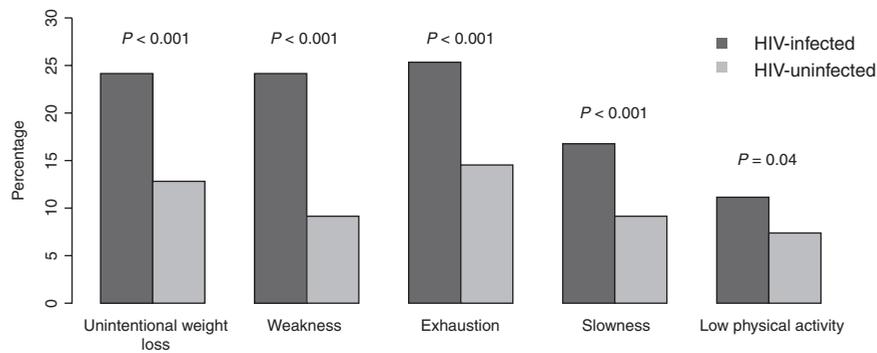


Fig. 2. Prevalence of frailty criteria.

independently associated with a higher OR for a higher frailty category, nor were the nadir or current $CD4^+$ cell count, having a detectable viral load in the year prior to enrollment, the known duration of HIV-1-infection or a history of AIDS.

However, following adjustment for current BMI less than 20 kg/m^2 and WHR as well as nadir BMI less than 20 kg/m^2 , the ORs of both protease inhibitor exposure and time spent with a $CD4^+$ cell count less than 200 were slightly attenuated and no longer statistically significant (OR for a $CD4^+$ cell count <200 1.09/year, 95% CI 0.95–1.24, $P=0.21$ and OR for the duration of protease inhibitor exposure 1.03/year, 95%CI 0.99–1.08, $P=0.14$).

Table 3. Multivariable ordinal logistic regression model, with prefrailty and frailty as outcome.

	OR (95%CI)	P-value
HIV-infected status	1.65 (1.24–2.20)	0.001
Age		
45–50 (reference)	–	–
50–55	1.05 (0.74–1.47)	0.79
55–60	1.47 (1.00–2.16)	0.05
60–65	1.45 (0.94–2.25)	0.10
>65	4.10 (2.53–6.64)	<0.001
Male sex	0.54 (0.34–0.85)	0.008
Black race/ethnicity	1.35 (0.84–2.17)	0.22
Smoking		
Ex-smoker	1.23 (0.90–1.67)	0.20
Current smoker	1.36 (0.98–1.91)	0.07
HCV (co)infection		
Cleared	1.70 (0.83–3.46)	0.15
Chronic	5.26 (2.06–13.48)	0.001
Depressive symptoms		
CES-D 16–24	4.57 (3.00–6.94)	<0.001
CES-D ≥ 25	6.25 (3.43–11.36)	<0.001
WHR, per 0.1 increase	1.60 (1.30–1.97)	<0.001
BMI $<20 \text{ kg/m}^2$		
For HIV-infected individuals	6.14 (3.10–12.18)	<0.001
For HIV-uninfected individuals	0.67 (0.21–2.19)	0.51

CES-D, Center for Epidemiologic Studies Depression; HCV, hepatitis C virus; WHR, waist-to-hip ratio; Age, sex and race/ethnicity were forced into the model; all variables listed in Table 2 that were independently associated with a higher frailty category and/or significantly affected the association between HIV-status and a higher frailty category are included in the final model.

A current BMI less than 20 kg/m^2 (OR 2.83, 95%CI 1.26–6.37, $P=0.01$), a nadir BMI less than 20 kg/m^2 (OR 2.51, 95%CI 1.46–4.31, $P=0.001$) and a higher WHR (OR 1.79 per 0.1 higher, 95%CI 1.32–2.41, $P < 0.001$) were most strongly associated with a higher frailty category in the multivariable model.

Further adjustment for the number of diagnosed AANCC and hsCRP, D-dimer, sCD163 and sCD14 levels did not significantly affect these associations.

Discussion

We investigated the frailty phenotype in a population of middle-aged HIV-infected individuals, predominantly with undetectable HIV viral load on cART, and similar HIV-uninfected controls. Depression, low BMI and higher WHR were strongly associated with a higher frailty category, but none of the investigated factors could fully explain the observed association between HIV infection, prefrailty, and frailty. Markers of inflammation and immune activation were not associated with a higher frailty category. Currently having a low BMI ($<20 \text{ kg/m}^2$) was significantly associated with a higher OR for a higher frailty category in the HIV-infected, but not in the HIV-uninfected group. Within the HIV-infected group, longer time spent with a $CD4^+$ cell count less than 200 and longer protease inhibitor exposure were associated with a higher OR for a higher frailty category, but this was no longer statistically significant after adjusting for low current and nadir BMI ($<20 \text{ kg/m}^2$) and WHR.

The higher prevalence of frailty and prefrailty in HIV-infected compared with uninfected individuals we observed confirms earlier studies [3–7]. The majority of HIV-infected individuals were on long-term cART, enabling us to investigate (determinants of) frailty in treated HIV in more detail. Furthermore, inclusion of a highly comparable control group and collection of detailed information on demographics, behavior,

comorbidities, body composition and HIV- and ART-history, enabled us to further explore the pathogenesis of frailty in HIV-infected individuals.

In the general as well as in the HIV-infected population markers of inflammation have been associated with frailty [2,11,14]. As (treated) HIV infection is associated with a pro-inflammatory state [24], we explored the involvement of inflammation in the pathogenesis of frailty. We confirmed HIV-infected participants to have higher levels of markers of inflammation and immune activation, but these were not independently associated with frailty. However, our information was limited to the current levels of a selection of inflammatory markers. Interleukin-6, a marker previously associated with frailty [2,14], was not measured. Furthermore, levels of inflammation may have been higher before the start of cART. Therefore, our results are not conclusive in excluding a role of inflammation in the pathogenesis of frailty.

Depression may be a consequence of as well as a contributor to frailty [25]. Considering the bidirectional relation between frailty and depression, adjusting for depression is likely an overadjustment. Furthermore, even though depression was more common in the HIV-infected group, adjusting for its presence only moderately affected the association between HIV and (pre)frailty (<10%). This indicates that in our HIV-infected population the higher prevalence of frailty cannot be solely explained by the higher prevalence of depression.

Chronic HCV infection was independently associated with (pre)frailty. This is consistent with a study associating HCV infection with an increased risk for frailty incidence in HIV-infected and uninfected individuals [7]. We did not find a statistically significant interaction between HCV and HIV infection. However, the number of HCV-infected study participants was small. Whether the effect of HCV infection differs according to HIV serostatus therefore deserves further study in a population with a higher prevalence of chronic HCV (co)infection.

Obesity, specifically abdominal obesity, has been recognized as risk factors for the development of frailty in the general population [15,16,26]. Mechanistically, low level systemic inflammation and oxidative stress are hypothesized to be involved [15]. One small study of HIV-infected people, but without controls, showed an association between a high BMI, abdominal obesity and frailty [17]. In the aging HIV-infected population abdominal obesity may partly be due to normal physiological aging and partly from body composition changes due to exposure to HIV and ART, including current regimens [18,27,28]. In our cohort the WHR was more strongly associated with frailty than abdominal obesity, as indicated by waist-circumference, or generalized obesity as indicated by the BMI. Furthermore, a higher WHR appeared to mediate the relation between

HIV-infected status and frailty. This suggests that not only abdominal fat accumulation (of which high waist-circumference is an accepted surrogate), but also peripheral lipoatrophy (which may result in a reduced hip-circumference) may contribute to the development of frailty in the context of treated HIV infection. Alternatively, the lower hip-circumference may be related to muscle loss or sarcopenia, an important contributor to frailty [1].

In the HIV-infected but not uninfected participants, a current BMI less than 20 kg/m² was strongly associated with a higher frailty category. Low BMI has been associated with frailty previously in the general population [15] as well as in HIV-patients [5,21]. The lack of an association in the HIV-uninfected group may partially result from the relatively low proportion of individuals with an extremely low BMI in our cohort and partially from the different meaning of a low BMI in HIV-infected individuals. In the HIV-infected population a low BMI may be a persistent consequence of advanced HIV-disease and related weight loss, whereas in HIV-uninfected individuals a relatively low BMI may be an expression of a lean healthy build. An additional argument in support of this hypothesis is the observed association between nadir BMI and a higher frailty category in the HIV-infected group, even in individuals with a currently normal BMI (possibly having recovered after cART initiation).

Several studies have demonstrated associations between markers of current HIV-disease severity, such as clinical AIDS and immunodeficiency, and frailty [4,8]. In our population only 5.6% of the HIV-infected individuals were not currently on cART, and the majority had a CD4⁺ cell count above 500. Therefore, the statistical power to detect differences according to current HIV-disease status was limited. We did, however, observe an association between the duration of time spent with a CD4⁺ cell count less than 200, and a higher frailty category. This association was attenuated after we adjusted for covariates related to current and historically low BMI, possibly indicating that the observed association is rather a consequence of HIV-disease-related weight loss than of immunodeficiency itself. A previous study found a lower nadir CD4⁺ cell count in frail compared with nonfrail individuals [21], but in that study information regarding historical BMI was unavailable. To our knowledge, no previous studies have reported on the association between historical low BMI and frailty in HIV-infected individuals.

This study is subject to several limitations. Due to the observational character, it is impossible to draw definite conclusions on the associations between use of specific types of ART and frailty; we can only speculate and form hypotheses to be confirmed in longitudinal studies and randomized controlled trials. One previous study has reported frailty to be associated with current protease

inhibitor exposure; however, this analysis was unadjusted [21]. The attenuation of the association between duration of protease inhibitor exposure and frailty by adding WHR to the model, may suggest some mechanistic role for protease inhibitor-associated body composition changes, either lipohypertrophy or lipotrophy or both. We used adaptations of two of the Fried phenotype criteria; we classified slow walking speed and low grip strength by the per stratum lowest quintile of the study population rather than using the predefined cut-offs based on per stratum lowest quintiles in a population of elderly individuals from the original paper by Fried *et al.* [1]. In this way we avoided a ceiling effect, as generally grip strength and walking speed are higher in middle-aged than in elderly individuals. As a consequence, frailty according to our definition is not directly comparable to that used in some other cohorts; however, as our objective was to compare HIV-infected and HIV-uninfected individuals within the same cohort this does not affect our results. Populations of HIV-infected individuals generally are younger than the population the frailty phenotype has been developed in; the clinical consequences of frailty in this relatively young population are largely unknown. Few studies have prospectively investigated consequences of frailty in HIV infection, but these were conducted in specific populations, limiting the generalizability of their results. A study among intravenous drug users found frailty to be associated with mortality [6] and an adapted frailty phenotype was associated with AIDS and mortality among ART-naïve HIV-infected individuals [29] and with hospitalization and mortality in HIV-infected and HIV-uninfected veterans [30]. Additionally, frailty defined as the number of accumulated deficits predicted mortality and multimorbidity in HIV-infected individuals [31]. Ongoing longitudinal follow-up of the AGE_hIV Cohort Study will provide more information on the prognostic value of the frailty phenotype in these middle-aged HIV-infected and HIV-uninfected individuals.

In conclusion, the higher prevalence of frailty and prefrailty in HIV-infected participants of the AGE_hIV Cohort Study could not be explained by comorbid conditions, depression or levels of inflammation. Exposure to severe immunodeficiency and being underweight appear to play a role in the pathophysiology of frailty in the context of HIV. Therefore, frailty may in part be a long-term consequence of having experienced advanced HIV-disease. As this can be avoided by timely initiation of cART, one may expect individuals who are diagnosed and treated earlier in infection to be less affected by frailty. The higher waist- and lower hip-circumference in HIV-infected study participants may partly have resulted from body composition changes due to exposure to HIV or ART, also in more recently infected individuals and those treated with modern cART. The observed association between greater WHR and a higher frailty category, which in part explained the association between HIV-infection and frailty, thus

suggests that body composition changes may also have contributed to the onset of frailty.

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Conflicts of interest

K.K. has received travel grants from Gilead Sciences and ViiV Healthcare, and was a speaker at an event sponsored by Gilead Sciences for which her institution received remuneration.

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