Frailty in HIV-infected adults in South Africa

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Abstract

Objectives—Some evidence suggests that HIV infection is associated with premature frailty -a syndrome typically viewed as being related to ageing. We determined the prevalence and predictors of frailty in a population of HIV-infected individuals in South Africa.

Design—Case-control study of 504 adults over the age of 30 years, composed of 248 HIV-infected adults and 256 age- and gender- frequency-matched HIV-seronegative individuals.

Methods—Frailty was defined by standardized assessment comprised of ≥ 3 of: weight loss, low physical activity, exhaustion, weak grip strength and slow walking time. Independent predictors of frailty were evaluated using multivariable logistic regression.

Results—The mean ages of the HIV-infected and HIV-seronegative groups were 41.1±7.9 years and 42.6±9.6 years respectively. Of the HIV-infected adults, 87.1% were receiving antiretroviral treatment (ART) (median duration, 58 months), their median CD4 count was 468 cells/μL (IQR: 325-607 cells/μL) and 84.3% had undetectable plasma viral load. HIV-infected adults were more likely to be frail than HIV-seronegative individuals (19.4% vs.13.3%;p=0.07), and this association persisted after adjustment for confounding variables (adjusted odds ratio [OR] 2.14; 95% confidence interval [95%CI]: 1.16-3.92, p=0.01). Among HIV-infected individuals, older age was a strong predictor of frailty, especially among women (women: OR=2.55 per 10-year age increase; men: OR=1.29 per 10 year age increase, p-interaction=0.01). Lower current CD4 count (<500 cells/μL) was also independently associated with frailty (OR=2.84;95%CI:1.02-7.92, p=0.04).

Conclusion—HIV infection is associated with premature development of frailty, especially in women. Since higher CD4 counts were associated with lower risk of frailty, earlier initiation of ART may be protective.

Introduction

Major reductions in HIV-associated mortality have occurred as a result of the global scale-up of highly active antiretroviral therapy (ART). This is largely due to prevention of AIDS-related events but is also due to a decrease in non AIDS-related events and deaths.[1-3] Despite these benefits, evidence is emerging that patients receiving ART are at an increased risk of age-related non-AIDS morbidity and mortality compared with HIV-seronegative individuals.[4-6] Several of these conditions are classically associated with the normal ageing process but appear to occur at an earlier age in HIV-infected persons compared to age-matched HIV-seronegative individuals. It is possible that not only are HIV cohorts ageing chronologically, but they may also be undergoing accelerated physiological and immunological senescence.

Frailty is a clinical syndrome initially described in geriatric populations. It reflects a concept of decreased physiological and functional reserve and a subsequent decrease in adaptation to external or intrinsic stressors. Frailty is characterised by multiple pathologies, low physical activity and slow motor performance,[7,8] and leads to cognitive and physical decline manifest as an increased risk of mortality, falls and hospitalization. HIV infection has been associated with premature development of frailty and it has been speculated that this may emerge as an important clinical syndrome in HIV-infected individuals. The prevalence of premature presentation of frailty in HIV-infected populations is reported to range between 5 and 20%, depending on the study population.[9-12] However, limitations of these reports include studying single sex cohorts and differences in frailty criteria. There is also substantial potential for confounding due to differential exposure to potential risk factors between the study population and the reference uninfected population (if used), thereby altering their risk of age-related outcomes.

The epidemiology of HIV and AIDS in sub-Saharan Africa is changing; extensive ART scale-up has led to reduced mortality rates and a rapidly expanding cohort of HIV-infected African patients who are living much longer than previously.[13,14] However, it is unclear whether these individuals will also be subject to premature ageing in the longer term. Estimates from previous studies from Europe and North America where the epidemiology of HIV differs substantially from that in sub-Saharan Africa, may not be generalizable to African HIV cohorts. In this study, we determined the prevalence and predictors of frailty in an HIV-infected population in sub-Saharan Africa.

Methods

Study participants

Between March and December 2011, unselected HIV-infected individuals of more than 30 years of age were enrolled from a community-based HIV treatment centre in Nyanga district of Cape Town which has been previously described.[15,16] All participants had a confirmed serological diagnosis of HIV and were either about to commence ART (ART-naïve), or were already on first-line ART. Participants who had active opportunistic infections (OIs)

were not recruited; however participants who had active TB (i.e. non-symptomatic but still receiving treatment for TB) were enrolled.

A control group of HIV-uninfected participants was recruited using frequency-matching by gender and 5-year age categories. HIV-seronegative individuals were enrolled from participants confirmed to be HIV-negative attending an HIV prevention trials site (Emavundleni Centre), located within the same district as the HIV treatment centre. These two centres were chosen as individuals attending them were drawn from the same community and were therefore likely to have similar socio-demographic characteristics.

The study was approved by the London School of Hygiene and Tropical Medicine Ethics Committee and the University of Cape Town Faculty of Health Sciences Research Ethics Committee, and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants

Assessment of frailty and data collection

Physical frailty was defined by the presence of 3 of 5 criteria: i) unintentional weight loss (Self-report of weight loss was verified in 100 (20%) participants by weighing of the participant at the time of data collection followed by referral to clinic records. Self-report and clinical records were congruent in 80 participants.) ii) self-reported low physical activity, iii) self-reported exhaustion, iv) weak grip strength and v) slow walking time (Appendix 1). All of these five components described in the original phenotype by Fried et al[17] were used to determine the presence of frailty. However, we used the proxy described by Önen et al[10] for the physical activity measure (see Appendix 1 for description). Grip strength of the dominant hand was measured three times using a grip dynamometer (Jamar Plus+ Digital Hand Dynamometer, Jamar, US). The average of three weight measurements was recorded in kilograms (kg) to one decimal point. Walking time was assessed using the method of Cesari et al.[18] The average of two trials (in m/s) was used for analysis. Participants were excluded from the determination of grip strength if they had pain or arthritis of the dominant hand, and excluded from the walking test if they had paralysis of an extremity or side of the body, or needed to use a walking aid.

Socio-demographic information and medical history were obtained via a questionnaire administered in the participant's first language (Xhosa or English). Socio-demographic and behavioural variables of interest included education, alcohol consumption, smoking history and income (salaried income and/or social welfare grant). Clinical information was obtained from medical case notes where required. Co-morbidity was defined as the concurrent presence of one or more chronic diseases or conditions including cardiovascular disease, chronic renal failure, airways disease and malignancy (both AIDS and non-AIDS defining). Cardiovascular diseases included myocardial infarction and cerebrovascular disease. Blood pressure (BP) was measured using a digital sphygmomanometer. Hypertension was defined as a systolic BP of 140 mmHg or higher, diastolic BP of 90 mmHg or higher, or the combination of self-reported high BP diagnosis and the use of anti-hypertensive medications. Height was measured in metres and weight in kg, and body mass index (BMI) was calculated as $weight/height^2$. HIV-related conditions were classified according to the WHO staging system and were based upon historical assessment done at the time of enrolment into the ART service. ART was defined as the use of 3 antiretroviral drugs, and treatment duration was recorded in months. Nadir and current CD4 count and HIV RNA plasma viral load (VL) were available from medical records, current values being measured within an 8-week period prior to frailty assessment. Viral load suppression was defined as HIV RNA <50 copies/mL.

Statistical analysis

Analyses were conducted on participants with criteria available for determination of frailty phenotype (3 or more of the criteria present). Participants were categorised as 'frail' and 'non-frail', using the criteria given above. Comparisons between categorical groups were performed using Chi-squared tests. Continuous variables were compared using Student's t-test if normally distributed and the Mann-Whitney U test if non-normally distributed. Variables were log transformed where appropriate. All p-values were 2-tailed and considered significant if p<0.05. Univariable logistic regression was performed to estimate odds ratio (OR) and 95% confidence intervals (CI) of factors associated with frailty. Multivariable logistic regression was then used to evaluate independent factors associated with frailty overall, and within the case and control groups, respectively. HIV-infected individuals were also analyzed based upon their ART status (naïve or on treatment). All analyses were performed with Stata 11 (Stata Corp., Texas, USA).

Results

Participant characteristics

Of the 504 participants, 248 had HIV-infection, and 256 were HIV-seronegative individuals. The two groups of participants were similar in terms of age and gender (Table 1), but HIV-infected individuals tended to have higher levels of education (87.9% vs. 81.6%, p=0.05), and reported lower levels of alcohol use and smoking consumption than HIV-seronegative individuals (p<0.05). HIV-infected individuals reported a greater income than HIV-seronegative individuals (41.6% vs. 32.0% received more than ZAR1000 a month (approx USD125), which was related to a greater proportion of the HIV-infected group receiving social welfare grants compared to HIV-seronegative individuals (data not shown). Although tuberculosis (TB) in the form of current or past disease was more common in the HIV group, other co-morbidity was slightly higher in the control group. BMI was lower in HIV-infected individuals compared to HIV-seronegative individuals (27.7 ± 6.5 kg/m^2 vs. 31.3 ± 8.8 kg/m^2, p<0.0001). Among females, HIV-infected individuals reported fewer pregnancies than HIV-seronegative individuals (p=0.006).

Clinical characteristics of the HIV-infected individuals are also reported in Table 1. Overall, 72.9% had a history of WHO stage 3 or stage 4 defining illness. The current CD4 count among participants receiving ART was 468 cells/μL (interquartile range [IQR], 325-607 cells/μL) and 84.3% had undetectable VL. Median treatment duration on ART was 58 months (IQR: 34-75 months). 12.9% of the HIV-infected group were ART naïve, and had correspondingly lower CD4 counts and higher VL (Table 1).

Prevalence of frailty and association with HIV

Assessment of frailty was possible in all participants, (n=504, with 3 participants excluded from the walking test but still contributing frailty data). Frailty outcomes within the study population are reported in Table 2. The prevalence of frailty was greater among HIV HIV-infected individuals than HIV-seronegative individuals (19.4%, 95%CI: 14.4-24.3% vs. 13.3%, 95%CI: 9.1-17.5%; p=0.07). Levels of 'pre-frailty' (i.e. scoring one or two of the frailty criteria) were similar between the two groups. Of the frailty indicators, weight loss and slow walking time were more common in the HIV-infected group, however these differences did not reach statistical significance.

Multivariable analysis adjusting for baseline characteristics and *a priori* confounders showed that HIV infection was independently associated with frailty (adjusted odds ratio [OR] 2.14; 95%CI: 1.16-3.92; Table 3). Age was also a strong predictor, and this association was stronger in females (p-interaction=0.03). A higher level of education reduced the odds of

frailty (OR=0.44; 95%CI: 0.21-0.90). Low BMI was also strongly associated with frailty. TB was not included in the model due to its high correlation with HIV status. When TB was analyzed as a potential binary outcome of interest (no history vs. current/past) the association with frailty was not as strong as that for HIV (OR 1.73; 95%CI: 0.94-3.08) and did not reach statistical significance.

Predictors of frailty in the HIV-infected group

Among the 216 HIV-infected individuals on ART, the prevalence of frailty was 18.0% (95% CI: 13.2-23.8%). In univariable analyses, older age and lower socioeconomic status, (including education level) and alcohol consumption were associated with higher odds of frailty.

In the multivariable model, there was evidence of an interaction between gender and age with a strong association between increasing age and frailty within females but not males (p for interaction =0.001). Low BMI was also a strong predictor of frailty (p trend=0.01). Among the HIV-related covariates, a current CD4 count less than 500 cells/µL was associated with increased risk of frailty (OR=2.84; 95% CI: 1.02-7.92). No associations were found with HIV RNA levels (current or nadir), duration of treatment or ART regimen. Socio-economic variables were not associated with frailty in this model. In a multivariable analysis restricted to females on ART, a similar association was seen with current CD4 count. Age continued to act as a strong predictor as well as low BMI. A history of three or more pregnancies was also associated with frailty in this group (OR 3.42 [1.03-11.36], p=0.04) (data not shown).

In the ART naïve group (n=32), 28.1% (95% CI: 13.7-46.7%; n=9) were frail. The only factor associated with frailty in a multivariable analysis was WHO clinical stage 3 or 4. Age and gender and other HIV-related covariates were not associated.

To assess the possibility of current diagnoses of TB (the most common opportunistic infection in this setting)[15] causing false misclassification of frailty, we constructed a separate multivariable model excluding such patients (n=10). In this model HIV still remained strongly predictive of frailty (OR=2.08; 95%CI: 1.12-3.86, p=0.02). In a further model of HIV-infected participants that similarly excluded those with a current diagnosis of TB, CD4 count remained a strong predictor of frailty (OR=2.89; 95%CI: 1.04-8.00, p=0.04).

Predictors of frailty in the control group

Among HIV-seronegative individuals, frailty was independently associated with older age, female gender and smoking (Table 5). There was also some evidence that TB was associated with frailty. In view of the strong association of female gender with frailty we performed sub-analyses restricted to females. In adjusted analyses, increasing age was still a strong predictor of frailty.

Discussion

This study provides clear evidence that HIV infection is strongly associated with a two-fold risk of premature frailty in this African population. Premature frailty was most prevalent in women who comprise the majority of the HIV-infected population in sub-Saharan Africa. These findings have potentially important implications for long-term morbidity among the millions of patients receiving ART long-term in Africa, and may have an important bearing on the optimum timing of ART initiation.

Our HIV-related frailty prevalence of 19.4% is higher than estimates from other regions. A prevalence of 9% was reported from a clinic population in the United States (US) (mean age

42 years).[10] The Women's Interagency HIV Study (a prospective cohort in five US cities) found a prevalence of 12% in HIV-infected women with clinical AIDS (median age 41 years).[11] In the Multicenter AIDS Cohort Study (MACS) (a longitudinal study of men who have sex with men), a frailty prevalence of 5-14% depending on age and duration of HIV infection was reported from 1994-2005 data,[9,12] and 8% in 2009-2010 among men aged 40-49 years.[19] In the SUN study (a US observational cohort of HIV-infected adults, median age 47 years), 5% of participants were frail.[20] The variation in estimates is likely to be attributable to differences in study design and clinical demographics of patients recruited (e.g. ART status, degree of immunodeficiency).

In agreement with previous studies of participants on ART, current CD4 count was a strong, independent predictor of frailty. [9,11,12,19] However, we did not find an association with duration of ART or nadir CD4 cell count. These findings are entirely consistent with previous analyses of factors associated the risk of incident TB risk and of mortality in this cohort.[21,22] Thus, although these three variables are inter-related,[23] it seems that current CD4 count best captures current 'well-being' in this ART cohort. Thus, the best way to prevent frailty may be to maintain high CD4 counts through early initiation of ART. Potential reductions in non-AIDS-related morbidity and mortality from earlier initiation of ART are currently under investigation in the Strategic Timing of AntiRetroviral Treatment (SMART) study[24] and prevention of frailty may be another important benefit of such a strategy.

It is possible that frailty status could be misclassified in some HIV-infected participants due to recent or current opportunistic infections. However, we think this unlikely for several reasons. Participants with acute symptomatic OIs were not eligible for enrolment in the study and a large majority of patients were clinically stable on long-term ART (median 58 months). They had a median CD4 count of 468 cells/μL and so were at low risk of current co-morbidity, and previous WHO stage 3 and 4 defining illnesses were remote. A small number of participants had current diagnoses of TB for which continuation phase treatment was being received. Estimates of HIV as a predictor of frailty did not greatly change when these participants were excluded from analyses suggesting that misclassification was minimal. Thus we believe that the observed association of frailty with the HIV-infected group is likely to be related to HIV infection itself rather than as a consequence of symptoms related to current OIs.

Female gender was an important predictor of frailty in both study populations. In the general population, frailty is more common among females.[25,26] Men may be protected by greater muscle mass and higher testosterone levels[27] reflecting the greater biological capital they achieve before age-related decline. Two US-based studies did not find an association of female gender with frailty,[10,20] possibly due to the gender composition (predominantly male) of the study populations or reduced statistical power to detect an interaction. The interaction of gender and age in the HIV-infected group in our study is a novel finding. This interaction may be related to effects of decreased circulating oestrogens with increasing age and subsequent inflammation. In physiological ageing, low levels of oestrogens may be associated with increased levels of pro-inflammatory cytokines that have been linked to sarcopenia.[28] This effect may be exacerbated or modulated by HIV infection or ART. In resource-constrained settings it is possible that women are nutritionally deficient compared to men, exacerbated by multiple pregnancies.

In sub-Saharan Africa, the proportion of elderly people infected with HIV is increasing.[13] In 2007, approximately 3 million people aged >50 years were living with HIV in sub-Saharan Africa, comprising 14% of the adult HIV population.[30] With 5.1 million people in sub-Saharan Africa having started ART by the end of 2010, the number of people aged >50

years living with HIV will inevitably continue to increase.[31] These evolving demographics may necessitate a shift from treatment of primarily opportunistic infections towards management of non-AIDS related conditions. Furthermore, if premature ageing is scientifically validated, HIV-infected patients >50 years of age may come to be considered 'old'.[32] Chronic age-related disease within African HIV-infected populations is likely to place a significant burden on healthcare budgets and human resources. The high prevalence of HIV-related frailty also has additional economic implications. Those who are frail are less likely to be economically productive and more likely to need assistance from families and welfare grants. Interventions to improve frailty may be simple such as progressive resistance exercises. This intervention improved the strength of HIV-infected adults in Brazil.[33] However, given the multi-factorial aetiology of frailty, other systemic mechanisms may also require intervention.

A key strength of this study is the inclusion of an age/gender matched control group with a similar socio-demographic profile as the HIV-infected individuals. The hypothesis of premature ageing in HIV has received criticism primarily due to limitations in characterization of participants, in particular the possibility of differential exposure to potential risk factors between HIV-infected and uninfected populations.[32,34,35] For example, in the US Veterans Aging Cohort HIV-infected veterans were more likely to have a history of substance misuse compared to age- and sex-matched uninfected veterans.[36] The differential exposures to risk factors between HIV-infected and uninfected populations and residual confounding could result in an apparent increased risk of age-related outcomes. By recruiting from the same community, we aimed to reduce the likelihood of differential risk exposure. Compared to HIV-seronegative individuals, the HIV-infected group in this study tended to be more affluent (likely reflecting receipt of welfare grants) and also more educated as has been observed elsewhere in South Africa.[37] HIV remained strongly associated with frailty even after adjustment for socioeconomic factors.

This study has some limitations. We studied a frailty-like phenotype rather than the previously defined and validated frailty phenotype [17]. However, this modified phenotype is comparable to phenotypes employed in other studies of HIV-related frailty. [9,10,12] The frailty phenotype within the context of HIV has not been fully established or validated to date. The main limitation of the frailty criteria relates to their subjective nature. Grip strength and walking time measured at the time of data collection may not necessarily represent the participant's overall ability, and a longitudinal evaluation of these parameters would be optimal. Similarly, reports of exhaustion relied on self-report. The original phenotype used a weighted score of kilocalories expended to assess low physical activity. This may be difficult to ascertain in resource-limited settings, and the approximate adopted by Önen et al[10] may be more useful in these environments. Although we relied on self-report of weight loss, validation of a proportion of the reports was favourable and no differential misclassification between groups was observed.

The study design means that a causal relationship between HIV and frailty cannot be concluded, and nor can a temporal relationship be established. We are unable to infer whether HIV infection or ART is primarily responsible for the strong association with frailty, partly due to a low proportion of ART-naïve participants (12.9%). Often such patients are more acutely ill, and may be less willing or able to take part in research studies. In the MACS cohort, the presence of frailty prior to ART initiation was an independent predictor of the development of AIDS or death despite ART.[38] Thus, frailty status may assist in establishing risk of morbidity and mortality. In the current study we were unable to assess whether a diagnosis of frailty was related to outcomes typically associated with the syndrome in older adults, such as falls, hospitalisation and death. To fully assess if

individuals in sub-Saharan Africa meeting the definition of frailty are at increased risk of these outcomes will require longitudinal studies.

In conclusion, HIV is an important predictor of frailty in this African population. Sub-Saharan Africa is undergoing significant HIV-related demographic changes, leading to an ageing HIV-infected population. Chronic age-related conditions will impact this population and HIV-related premature ageing will likely compound this disease burden. Early initiation of ART at higher CD4 counts may maintain CD4 counts at higher levels and protect against development of the frailty phenotype. As access to ART expands, and patients continue to age and live with HIV infection, longitudinal studies are needed to assess the evolution of frailty within HIV-infected populations and its impact on morbidity and mortality.

Acknowledgments

Appendix 1: Frailty criteria and definitions

Adapted from Fried et al.[17] and Önen et al.[10]

Criteria	Definition			
Unintentional weight loss	>10 pounds weight loss documented in last year or 5% of previous year's body weight			
Low physical activity*	Participants answering 3 when asked whether their health limits vigorous activities such as running, lifting heavy objects 1= not at all, 2 = yes, limited a little or 3 = yes, limited a lot			
Exhaustion	Participants answering 2 or 3 to either one of two statements – "How often have you felt that:" a) Everything you did was an effort or b) I could not 'get going' 0 = rarely (<1 day), 1= some of the time (1-2 days), 2 = occasionally (3-4 days) or 3 = most of the time (5-7 days)			
Weak grip strength	Male BMI kg/m^2	Kg	Female BMI kg/m^2	Kg
	24	29	23	17
	24.1-26.0	30	23.1-26.0	17.3
	26.1-28.0	30	26.1-29	18
	>28	32	>29.0	21
Slow walking time	Male height (cm)	Seconds	Female height (cm)	Seconds
	173	7	159	7
	>173	6	>159	6

* Estimation of physical activity adopted from Önen et al.[10]; the estimation of physical activity described in the original phenotype used a weighted score of kilocalories expended

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Table 1

Characteristics of study population

Variable	HIV-infected (248) % (n)	HIV-seronegative (256) % (n)	P-value
Age (mean±SD)	41.1±7.9	42.6±9.6	0.07
Age (years) by group			
30-39	49.6 (123)	49.1 (118)	
40-49	33.1 (82)	32.8 (84)	0.09
50-59	15.3 (38)	14.5 (37)	
>60	2.0 (5)	6.7 (17)	
Male gender	26.6 (66)	25.0 (64)	0.68
Education			
< High school	12.1 (30)	18.4 (47)	0.05
Income			
<USD 125/month	58.4 (145)	68.0 (174)	0.03
Marital status			
Single	68.6 (170)	63.7 (163)	
Married	25.4 (63)	29.3 (75)	0.68
Divorced	1.6 (4)	2.3 (6)	
Widowed	4.4 (11)	4.7 (12)	
Housing			
Informal	47.2 (117)	40.6 (104)	0.14
Water supply			
Shared	74.2 (184)	73.8 (189)	0.93
Alcohol (amount per week)			
Nil	70.5 (172)	54.4 (136)	
Up to 1L/week	18.4 (45)	22.8 (57)	<0.0001
>1L/week	11.1 (27)	22.8 (57)	
Duration of smoking (years)			
Nil	84.7 (210)	72.3 (185)	
5yrs or less	2.4 (6)	7.4 (19)	0.008
6-15	3.2 (8)	7.0 (18)	
16-20	4.4 (11)	6.3 (16)	
>20	5.2 (13)	7.0 (18)	
Illicit drugs			
Ever taken	2.5 (6)	2.4 (6)	0.94
BMI (kg/m^2)	27.7±6.5	31.3±8.8	<0.0001
Co-morbidity			
None	64.5 (160)	56.3 (144)	
One or more	35.5 (88)	43.7 (112)	0.06
TB status			
No history	31.9 (79)	87.9 (225)	<0.0001
Current	4.0 (10)	0.4 (1)	
Previous	64.1 (159)	11.7 (30)	
Number of pregnancies (n=374)			
2 or less	62.1 (113)	47.9 (92)	
3	37.9 (69)	52.1 (100)	0.006

Variable	HIV-infected (248) % (n)	HIV-seronegative (256) % (n)	P-value
HIV characteristics (n=248)		**Median (IQR) or %(n)**	
WHO stage			
1/2	27.1 (67)		
3/4	72.3 (181)		
ART naïve	12.9 (32)		
CD4 count in ART naïve group (n=32)	182 (84-202)		
Log_{10}VL in ART naïve group (n=21)	4.88 (4.21-5.18)		
Current CD4 count in ART group	468 (325-607)		
Nadir CD4 count in ART group	128 (76-171)		
% with undetectable VL in ART group	84.3 (182)		
Peak Log_{10}VL in ART group	4.56 (3.84-4.98)		
Duration of ART, months	58 (34-75)		
ART Regimen			
Containing AZT/3TC	59.7 (129)		
Other	40.3 (87)		

Table 2

Frailty-related outcomes within study population

	HIV-infected (248) % (n)	HIV-seronegative (256) % (n)	P-value
Frailty levels			
Robust (0)	31.8 (78)	35.9 (92)	
Pre-frail (1-2)	49.2 (122)	50.8 (130)	0.16
Frail (3+)	19.4 (48)	13.3 (34)	
Overall frailty (3+ from 5)			
No	80.7 (200)	86.7 (222)	0.065
Yes	19.4 (48)	13.3 (34)	
Contribution to frailty criteria	**Frailty + HIV+ (48)**	**Frailty+ HIV− (34)**	
Exhaustion	95.8 (46)	94.1 (32)	0.72
Low physical activity	83.3 (40)	91.1 (31)	0.31
Weight loss	64.6 (31)	47.1 (16)	0.11
Weak grip strength	43.8 (21)	58.8 (20)	0.18
Slow walking time	58.3 (28)	47.1 (16)	0.31

Table 3

Multivariable logistic regression model to identify predictors of frailty in all study participants (n=504)*

Variable	OR	P
HIV	2.14 (1.16-3.92)	0.01
Sex		
Male	1	
Female	1.29 (0.41-4.08)	0.03 for interaction
Male: (per 10 year increase)	0.94 (0.41-2.15)	
Female (per10 year increase)	2.55 (1.75-3.71)	
Alcohol (amount per week)		
Nil	1	
<500mL	0.75 (0.22-2.60)	0.10
500mL-1L	0.57 (0.24-1.39)	
>1L	0.24 (0.08-0.77)	
Education		
< High school	1	
High school /college	0.44 (0.21-0.90)	0.02
BMI		
<20	1	
20-24.9	0.22 (0.08-0.61)	
25-29.9	0.21 (0.08-0.60)	0.02
>30	0.20 (0.07-0.58)	
BP		
None	1	
Hypertensive	0.83 (0.45-1.53)	0.54
Co-morbid condition		
No	1	
Yes	3.20 (0.76-13.50)	0.11
Duration of smoking (years)		
Nil	1	
5yrs or less	0.78 (0.15-4.04)	
6-15	2.70 (0.63-11.52)	0.37
16-20	2.48 (0.79-7.77)	
>20	0.76 (0.16-3.59)	
Income/month (ZAR)		
<USD 125/month	1	
>USD125/month	1.05 (0.58-1.90)	0.87
Occupation		
Unemployed/grant	1	
Employed	0.65 (0.35-1.20)	0.17
Housing		
Formal	1	
Informal	0.70 (0.40-1.24)	0.23

*
Adjusted for all variables displayed within table

BMI=body mass index; BP=blood pressure; USD= US dollars

Table 4

**HIV predictors of frailty in HAART HIV+ group (n=216) [**]

Variable	Unadjusted OR	P	Fully adjusted OR		P
Sex					
Male	1		Males	1	
Female	1.65 (0.68-4.00)	0.27	Female	0.66 (0.13-3.22)	
			Male (per 10 year increase)	0.37 (0.08-1.77)	
Age, years					0.01 (for interaction)
30-39	1				
40-40	1.10 (0.45-2.68)		Female per 10 year increase	2.50 (1.35-4.58)	
50-59	5.90 (2.40-14.48)	0.0008			
>60	2.36 (0.23-24.40)				
HIV-related characteristics					
WHO clinical stage					
1/2	1			1	
3/4	1.10 (0.47-2.57)	0.83		1.19 (0.26-5.38)	0.83
Duration of ART, months					
0-36	1			1	
36-72	0.42 (0.18-0.98)			0.49 (0.16-1.49)	
>72	0.80 (0.34-1.85)	0.11		1.03 (0.31-3.41)	0.30
Current CD4 count (cells/μL)					
<500	1.77(0.84-3.72)	0.12		2.84 (1.02-7.92)	
>500	1			1	0.04
Nadir CD4 count (cells/μL)					
<200	0.62 (0.23-1.69)	0.37		0.42 (0.11-1.56)	
>201	1			1	0.19
Current Log_{10}VL					
<10,000 copies	1			1	
>10,000 copies	0.82 (0.17-3.83)	0.80		0.41 (0.05-3.63)	0.40
Peak Log_{10}VL					
<10,000 copies	1			1	
>10,000 copies	1.39 (0.62-3.12)	0.42		2.38 (0.82-6.92)	0.11
ART Regimen					
Containing AZT/3TC	1			1	
Other	1.03 (0.51-2.10)	0.91		0.60 (0.24-1.51)	0.28
TB status					
No history	1			1	
Current infection	1.48 (0.15-15.66)	0.93		0.65 (0.02-17.61)	0.96
Previous history	0.96 (0.44-2.09)			0.89 (0.22-3.54)	
Demographic characteristics					
BMI (kg/m^2)					
<20	1			1	
20-24.9	0.60 (0.18-2.03)			0.29 (0.06-1.36)	

HIV-related characteristics				
25-29.9	0.53 (0.16-1.80)	0.48	0.18 (0.03-0.99)	0.01 *ptrend*
>30	0.38 (0.11-1.31)		0.09 (0.01-0.55)	
Co-morbid condition (non-HIV-related)				
No	1		1	
Yes	1.01 (0.48-2/15)	0.97	0.67 (0.25-1.77)	0.42
Income/month (US dollars)				
<USD 125/month	1		1	
>USD125/month	1.26 (0.63-2.53)	0.51	1.34 (0.57-3.16)	0.48
Occupation				
Unemployed/welfare grant	1		1	
Employed	0.50 (0.23-1.06)	0.07	0.54 (0.21-1.36)	0.23
Education				
< High school	1		1	
High school /college	0.33 (0.13-0.82)	0.02	0.76 (0.21-2.82)	0.69
Housing				
Formal	1		1	
Informal	0.91 (0.45-1.82)	0.78	0.52 (0.23-1.28)	0.16
Alcohol (amount per week)				
Nil	1		1	
<500mL	0.88 (0.18-4.32)		1.40 (0.15-12.18)	
500mL-1L	0.26 (0.06-1.15)	0.03	0.17 (0.03-1.10)	0.07 *ptrend*
>1L	0.15 (0.02-1.17)		0.08 (0.01-0.88)	
Duration of smoking				
Nil	1		1	
<10 years	0.47 (0.06-3.86)		1.20 (0.09-15.92)	
>10 years	0.67 (0.19-2.40)	0.62	0.78 (0.13-4.67)	0.95

[**] Fully adjusted model adjusted for all variables displayed within table

ART= anti-retroviral therapy; VL=viral load; BMI=body mass index; USD= US dollars; TB=Tuberculosis

Table 5
Predictors of frailty in uninfected control group (n=256) [**]

Variable	Unadjusted OR	P	Adjusted OR	P
Age, years				
30-39	1		1	
40-49	6.39 (1.74-23.41)		8.59 (2.03-36.32)	
50-59	14.20 (3.65-55.12)	<0.0001	8.71 (1.75-43.31)	0.0006 ptrend
>60	43.13 (9.71-191.40)		24.10 (3.19-182.20)	
Sex				
Male	1		1	
Female	3.95 (1.15-13.27)	0.03	11.03 (1.68-72.37)	0.01
Income/month (US dollars)				
<USD 125/month	1		1	
>USD125/month	1.82 (0.88-3.81)	0.10	0.92 (0.28-1.93)	0.88
Occupation				
Unemployed/ welfare grant	1		1	
Employed	0.45 (0.20-1.04)	0.06	0.64 (0.21-1.93)	0.44
Housing				
Formal	1		1	
Informal	0.48 (0.21-1.08)	0.09	0.45 (0.16-1.25)	0.13
Duration of smoking				
Nil	1		1	
<10 years	0.20 (0.02-1.53)	0.05	0.67 (0.13-3.52)	0.03
>10 years	1.71 (0.79-4.14)		6.01 (1.51-23.85)	
Alcohol (amount per week)				
Nil	1		1	
<500mL	0.98 (0.20-4.78)		1.04 (0.16-6.86)	
500mL-1L	0.61 (0.22-1.72)	0.12	1.31 (0.34-5.06)	0.92
>1L	0.27 (0.08-0.95)		0.67 (0.13-3.53)	
Education				
< High school	1		1	
High school /college	0.34 (0.16-0.77)	0.008	0.47 (0.17-1.32)	0.15
BMI (kg/m^2)				
<20	1		1	
20-24.9	0.35 (0.15-0.82)		0.07 (0.01-1.11)	0.64 ptrend
25-29.9	0.42 (0.19-0.94)	0.10	0.28 (0.03-2.39)	
>30	0.43 (0.21-0.90)		0.40 (0.05-3.11)	
TB status				
No history	1		1	
Current/Previous infection	1.68 (0.63-4.48)	0.29	3.65 (0.96-13.81)	0.06
Hypertension				
Normotensive	1		1	
Hypertensive	2.79 (1.31-5.93)	0.008	1.09 (0.38-3.09)	0.87
Co-morbid condition				
No	1		1	
Yes	4.8 (1.28-18.00)	0.02	3.04 (0.47-19.86)	0.24

[**] Fully adjusted model adjusted for all variables displayed within table BMI=body mass index; USD= US dollars; TB=Tuberculosis