Frailty prevalence and predictors in older adults with HIV

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Abstract

Background: Advances in HIV management have resulted in life expectancy gains and consequent ageing in people living with HIV (PLWH). Frailty represents a state of vulnerability to stressor events and is associated with adverse outcomes. Frailty has been demonstrated in PLWH at earlier ages and in higher prevalence than HIV-negative cohorts. A comprehensive evaluation of frailty and frailty correlates is lacking in a UK based HIV cohort.

Aims: To establish frailty prevalence for a cohort of older adults with HIV in Sussex, and describe associations between frailty and sarcopenia and potential biological, psychosocial and cognitive predictors.

Methods: 253 participants aged ≥50 (median 59.6) were recruited between October 2014-October 2015. Frailty was defined by modified Fried frailty phenotype including five criteria: exhaustion, low activity, weight loss, weak grip and slow walking speed. Presence of ≥3 denoted frailty, 1-2 pre-frailty and 0 robust. Associations with frailty were evaluated from demographic, clinical, psychosocial, neurocognitive and functional parameters. A subgroup of 108 underwent DXA scanning to assess for the presence of sarcopenia.

Results: 48/253 met frailty criteria, giving a prevalence of 19% (95% CI 14.6-24.3). A further 111/253 (43.9%) were prefrail and 94/253 (37.1%) robust. Frailty was associated with increasing age, number of comorbidities and worsening mood symptoms, but not HIV factors. Additional correlates with frailty included financial insecurity, smoking, number of non-antiretroviral medications, chronic pain, low physical activity, and elevated IL-6. In the DXA subgroup, low muscle mass was common at 50% with 20% meeting criteria for sarcopenia, which was associated with increased odds of frailty. Negative psychosocial resources and poorer cognitive performance were associated with frailty, with positive psychological traits potentially buffering against higher frailty states.

Conclusion: Frailty is common and occurs prematurely in older adults with HIV. Frailty was associated with predictors across biological, psychological and social parameters, suggesting a need to shift emphasis away from a purely biomedical approach to frailty in PLWH.

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Acronyms and definitions

5SST	5 times sit-to-stand
(c)ART	(combined) Antiretroviral Therapy
ADL	Activities of daily living
AIDS	Acquired immunodeficiency syndrome
CCI	Charlson comorbidity index
CD4	CD4+ cell count/mm^3
CD8	CD8+ cell count/mm^3
CDC	Centre for Disease Control (and prevention)
CES-D	Centres for Epidemiologic Studies Depression Scale
CIRU	Clinical Investigation and Research Unit
CKD	Chronic Kidney Disease
COWAT	Controlled Oral Word Association Task
DDI	Drug-drug interactions
DXA	Dual-energy X-ray absorptiometry
DFS	D-factor score
eGFR	Estimated glomerular filtration rate
EWGSOP	European Working Group on Sarcopenia in Older People
FFQ	Food Frequency Questionnaire
FI	Frailty Index
FP	Frailty phenotype
FRP	Frailty related phenotype
HADS	Hospital Anxiety and Depression Score
HANA	HIV-associated non-AIDS defining
HAND	HIV-associated neurocognitive disorders
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life

iADLs	Instrumental activities of daily living
IQ	Intelligence quotient
IQR	Interquartile range
LSNS-6	Lubben social network scale-6
MACS	Multicentre AIDS Cohort study
MCI	Mild cognitive impairment
MI	Myocardial infraction
MoCA	Montreal Cognitive Assessment
MM	Multimorbidity
MMSE	Mini Mental State Examination
MSM	Men who have sex with men
NART	National Adult Reading Test
NASTAL-3	National surveys of sexual attitudes and lifestyles (3rd edition)
NCI	Neurocognitive impairment
NICM	Non-infectious comorbidities
NP	Neuropsychological
pADL	Personal activities of daily living
PASE	Physical Activity Scale for the Elderly
PHE	Public Health England
PIL	Purpose in life
PLWH	People living with HIV
PM	Prospective memory
POPPY	Pharmacokinetic and Clinical Observations in People Over Fifty
PRMQ	Prospective and Retrospective Memory Questionnaire
PVD	Peripheral vascular disease
QOL	Quality of life
RM	Retrospective memory
RSCH	Royal Sussex County Hospital

SCA	Successful cognitive ageing
SD	Standard deviation
SF-12	Short form-12
SHARE	Study of Health, Aging and Retirement in Europe
SMART	Strategies for Management of Antiretroviral Therapy (study)
SOF	Study of Osteoporotic Fractures
SRT	Simple reaction time
START	Strategic Timing of AntiRetroviral Treatment (study)
STI	Sexually transmitted infection
TGUG	Timed get up and go
TIA	Transient ischaemic attack
TMT	Trail Making Test
VACS	Veteran's Aging Cohort Study
WIHS	Women's Interagency HIV Study

Preface

Approximately 102,000 people are infected with HIV in the UK, and the proportion of individuals accessing specialist HIV care aged over 50 has more than doubled over the last decade from 14-34% [1]. Furthermore, ageing gains are being seen in all regions, making HIV and ageing a global issue [2]. Modern management has shifted HIV into the chronic infection era. People living with HIV (PLWH), particularly those at older ages, are experiencing greater non-infectious comorbidities and complex health needs despite effective viral control [3–5]. Therefore, the challenges of managing this group are changing, and in recognition have been prioritised as a subject of biological, clinical and socioeconomic research [6–8]. Amongst others, the American National Institute for Health emphasised key issues of multi-morbidity, polypharmacy, complexity and preservation of function. They promote the role of geriatricians' expertise and geriatric concepts such as frailty in guiding research with aim of proactive prevention and preserving function over curing disease [8].

Frailty is a multidimensional syndrome, primarily seen at older ages that indicates loss of homeostatic reserve and vulnerability to adverse events, which has been found to be prevalent in PLWH [9–11]. The aims of this study are to evaluate the prevalence of frailty in a cohort of older adults living with HIV in the UK, and undertake a multi-dimensional assessment, akin to a comprehensive geriatric assessment to identify potential predictive and protective factors associated with frailty. This will allow an examination of frailty beyond the thus reported biomedical perspective, adding important new information on the role of sarcopenia and novel insights in to the role of psychosocial and cognitive factors. Identifying candidate predictors may help to identify those at risk of negative ageing within the heterogeneous HIV-positive population.

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Lastly and most importantly, I would like to acknowledge my gratitude to all the participants that took part in the study. Without them this piece of work would not exist.

Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed: 

Name: Thomas James Levett

Dated: 9th May 2017

Chapter 1 - Introduction

Over the past four decades HIV has been transformed from an untreatable and often fatal condition into a controllable chronic infection [3]. Patient survival attributable to the success of combined antiretroviral therapy (cART) regimes introduced in the mid1990s is certainly a driver of cohort ageing in people living with HIV (PLWH). This must be coupled with ongoing later life acquisition [12] and reduced incidence in younger individuals pushing the burden of disease towards older age [3].

1.1 Ageing demographics

The term ‘older’ poses challenges to patients, clinicians, researchers and policy makers as its meaning is often contextual, with no clear biological cut-off evident given the heterogeneous nature of human beings and ageing trajectories. In the context of HIV, those aged 50 years and over are considered ‘older’. This reflects the data collection cut-off utilised by the Centre for Disease Control (CDC) in the United States [13]. In support of this, there seems to be an increase in what might be considered age-related comorbidities [14,15], as well as higher rates of negative outcomes in the context of initiation of treatment [16] or new diagnosis at or above this age [17]. This cut-off is considered too low by some [18] so consensus surrounding this may change, especially as it fails to reflect what may be considered old in many countries.

The most recent report from Public Health England (PHE) utilising data to end 2015 estimates that the UK has 101,200 people living with HIV (PLWH). Of the 88,769 PLWH that are diagnosed and accessing HIV services 34% are aged over 50 years old. This proportion has increased from 14% in 2006, representing a disproportionate increase compared to other age groups as shown in Figure 1.1 [1]. This demographic shift is a global phenomenon. A 2013 UNAIDS report estimates that worldwide 4.2 million people are living with HIV aged ≥50, the vast majority of whom reside in low and middle income countries [2]. The US has the largest proportion of their HIV cohort represented by older adults, with 42% of those living with diagnosed HIV in 2014 aged ≥50 [19], with an anticipation that this will have increased to over 50% by the end of 2015 [20,21]. Further to this, Smit et al. conducted a modelling study using the Dutch ATHENA cohort, anticipating

that by 2030 73% of the treated HIV cohort will be aged ≥50, with consequent increases in comorbid diseases and co-medication use [22]. They comment that these projections could be extrapolated to HIV populations like that of the Netherlands, such as seen here in the UK.

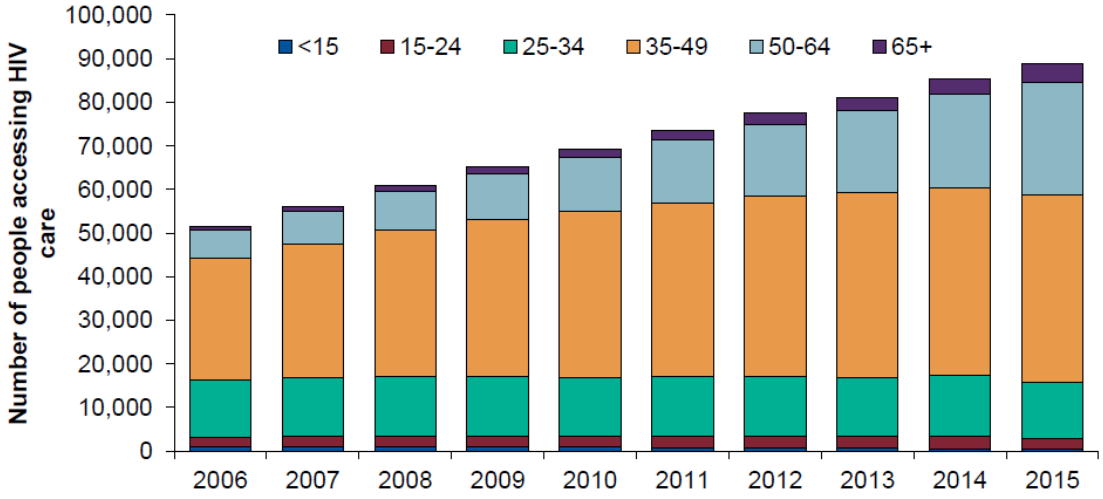


Figure 1.1: Public Health England data presenting people diagnosed with HIV accessing specialist care, by age group: UK, 2006-2015 [1]

1.2 Risk factors for HIV acquisition in older adults

HIV risk in older individuals is underestimated by both those at risk and by healthcare professionals that may encounter them [23,24]. Patient factors contributing to acquisition include ongoing sexual activity promoted or facilitated by increased later life divorce, use of the internet and social media [25], ease of international travel and possibility for sex tourism [26], and enhanced awareness and treatment of erectile dysfunction [23,25]. There is low perception or discussion of personal risk in individuals engaging in sexual intercourse particularly outside of traditional 'high risk' stereotypes [27–32]. These perceptions contribute to omission of condom use [33] alongside historical avoidance or lack of reproductive concern [23,34]. Lastly biological changes to the vaginal immune environment and mucosal thinning may make transmission more likely in women [8].

Professional factors may contribute through misperceptions about sexual practices, including acknowledgment that intercourse still continues at older ages [32,35,36]. Therefore, failing to reinforce safe sex messages or initiate testing for HIV and other sexually transmitted infections (STIs). Additionally, clinicians may be more likely to attribute symptoms of HIV-infection to other, more anticipated age-

related conditions [24]. Older individuals are also less likely to be offered proactive screening in areas with high HIV prevalence, where routine testing would be advocated [29], even though wide-spread testing is acceptable to patients [37].

More broadly, older adults risk exclusion in sexual health related social policy and prevention programmes [25,36,38–40], a reversal of which has been advocated by the authors of the third UK National Survey of Sexual Attitudes and Lifestyles (NATSAL-3) which includes adults up to the age of 74 [31].

These programmes could also be directed at older adults with HIV, who continue to engage in sex; with evidence reporting failure of disclosure of HIV status, concurrent acquisition of STIs and lack of consistent use of condoms or other risk management strategies that might contribute to onward transmission [41,42].

1.3 The effect of age on HIV

There are many relationships between chronological age and HIV, with age of acquisition being particularly important. Studies and epidemiological data suggest that people aged 50 and over are more likely to present later with their HIV [12,16,17,43,44]. Late diagnosis is defined variably but often taken as a presenting CD4 cell count below 350 cells/mm^3, which was the previously recommended point to initiate cART in the UK [45]. This has been demonstrated in the local Brighton cohort, where an examination of late presentation in service users diagnosed between 1996 and end 2010, showed that age ≥50 was associated with a more than doubled risk of late presentation (OR = 2.18; 95%CI: 1.52-3.12) [46]. This study demonstrated that although the proportion of those diagnosed late aged under 50 reduced from 57.1% to 38.5% over the period of interest, it remained static at between 60-65% if older [46]. This is significant as late diagnosis is associated with adverse outcomes including progression to AIDS and mortality [47], particularly at or around the time of diagnosis [18,43,48]. Age at diagnosis [17] and age at initiation of cART [49,50] are risk factors for increasing mortality irrespective of presenting CD4 count. These findings may be ameliorated by new guidance based on results of the Strategic Timing of AntiRetroviral Treatment (START) trial, in which traditional deferred cART initiation was associated with higher rates of non-AIDS events, AIDS diagnoses and mortality compared to immediate initiation of cART irrespective of CD4 count, which is now being advocated [51].

At initiation of cART older adults tend to have lower CD4 counts and higher viral loads than their younger counterparts [43,52]. There have been mixed reports of the immunological and virological outcomes achieved with cART in this group [53]. Older adults appear to have as good, if not better viral suppression compared to younger individuals [16,18,54,55], which is thought to be mainly secondary to better adherence in this age group [56,57]. There may also be better engagement with care generally as older adults have been shown to be more reliable attenders of HIV follow-up [18]. However, there seems to be a blunted immune reconstitution, with older adults failing to achieve equivalent CD4 counts [16,49,55,58,59]. Though others have shown no difference in virological suppression and CD4 immune recovery between older and younger groups [60].

1.4 Life expectancy in people living with HIV

UK life expectancy has continued to climb with an Office of National Statistics' report predicting a life expectancy from birth of 78.7 years for men and 82.6 for women [61]. Clearly one of the significant factors in HIV cohort ageing is enhanced survival and higher life expectancy. There has been contention about the influence that HIV has on life expectancy with previous reports suggesting reductions of around 10 years and others reporting a near normal life expectancy [48,62].

The most recent data from the UK Collaborative HIV cohort (UK-CHIC) including 21,833 individuals commencing cART from 2001 onwards examined mortality in relation to HIV control. They demonstrated that those achieving viral suppression and CD4>350 within a year of treatment initiation could expect a normal life expectancy [63]. This was supported by two separate studies by Lewden et al. and Rodger et al. who showed that in those reaching CD4≥500 the standardised mortality ratio compared to the general population approached 1, suggesting no excess mortality [64], with the latter study demonstrating an excess mortality for those with current CD4 between 350 and 499 [65]. It may be aspirational to aim for CD4 counts >500 on ART given these results, and that it represents what might be considered (lower end) normal in the absence of HIV [3]. Conversely however, a study of well-treated PLWH aged ≥50 with no comorbidity demonstrated an

excess in mortality compared to population controls with mortality rate ratio of 1.7 (95%CI:1.2-2.3) [66].

There had been debate as to whether HIV itself or the long-term sequelae of cART would pose greater problems for PLWH and as such the Strategies for Management of Antiretroviral Therapy (SMART) study randomised individuals with CD4 counts >350 to drug conservation with interrupted cART therapy (stopping cART until CD4 <350 or symptoms) versus continued therapy with viral suppression. The study was closed early in 2006 as significantly more primary outcome events of death from any cause and/or opportunistic infection were observed in those with interrupted cART. This was predominantly due to declines in CD4 and increases in viral load, thus advocating continued cART once initiated [67]. Excess deaths and reduced life expectancy have been demonstrated where HIV control is inadequate elsewhere [63,68].

HIV may not be the biggest driver of excess mortality in these individuals and the contribution of comorbidity and adverse lifestyle risk factors must be considered. In a Danish cohort study, individuals with well-controlled HIV and no comorbidity or concordant drug and alcohol abuse had equal life expectancy to those without HIV, though the effect of smoking could not be assessed [68]. A second Danish cohort study did examine the role of smoking on mortality in those with and without HIV, demonstrating that smoking contributed more to number of years lost than HIV infection itself [69].

1.5 HIV and comorbidity

With the advent and sequential improvements of cART we have seen a shift in comorbidities experienced by PLWH. With those in the pre-ART era experiencing high levels of opportunistic infections and AIDS-defining conditions, through to metabolic and clinical adverse events associated with early antiretrovirals such as lipodystrophy and painful neuropathies [3]. The current situation is one in which we see predominantly non-infectious comorbidities (NICM), which may have HIV and/or cART as aetiological risk factors, but are also conditions associated with general population ageing such as hypertension, cardiovascular disease, chronic kidney disease, depression, osteoporosis and non-HIV related cancers [3]. These

NICMs are of great importance as they have taken over as the leading cause of morbidity and mortality in PLWH [65,70]

Comorbidities in PLWH have been widely investigated in recent years. The non-controlled Swiss cohort study showed an increased number of incident non-AIDS diagnoses, including cardiovascular and thromboembolic events, diabetes, fracture and non-AIDS malignancies in PLWH over 50 compared to those under; with increasing incidence of comorbidity and death at higher ages and lower CD4 counts [71]. Using population registry data to represent an HIV-uninfected cohort, Guaraldi et al. demonstrated increased prevalence of a number of similar comorbidities in PLWH drawn from an HIV service specialising in metabolic diseases [72]. This corresponds to that seen in the Veterans Aging Cohort Study (VACS) [73]. Criticism has been placed on the lack or appropriateness of control groups. Therefore, the Dutch AGEhIV cohort study examined ageing-associated comorbidities and organ dysfunction in PLWH aged ≥45 compared to age and gender matched controls drawn from sexual health clinics in an attempt to capture similar risk profiles. Here, those with HIV had a significantly higher mean number of NICM compared to HIV-negative, which increased with age. For each NICM examined the prevalence was higher if HIV-positive, significantly so for myocardial infarction (MI), hypertension, peripheral vascular disease (PVD) and chronic kidney disease (CKD) [5]. Much work has focussed on the role of cART in NICM, with interrupted cART hypothesised as a method of reducing their incidence, however this was not demonstrated in the SMART study where lower rates of NICM and NICM-related deaths were seen in the group with continued cART use, suggesting that these events are related to level of immunodeficiency [67]. As such, HIV-associated risk factors that may predict the development of comorbidities include longer duration of HIV, exposure to first generation ART, low nadir CD4 or current CD4 <500, a low CD4/CD8 ratio (<1), detectable viraemia and history of AIDS-defining event or lipodystrophy [74]. In addition to predicting the presence of NICM, viraemia has been associated with poorer control of glycaemia and blood pressure in those with coexistent diabetes and hypertension [75].

Many studies have examined comorbidities in isolation, whether that be to investigate the role of HIV or antiretroviral toxicities in driving particular single organ disease states such as cerebrovascular disease [76], diabetes [77], CKD [78], ischaemic heart disease [79] or osteoporosis [80] or to examine the effect of HIV on NICM when compared to HIV-negative cohorts. This approach fails to recognise the complexity of comorbidity, in that individuals often exhibit more than one NICM, which may have wider implications in relation to cause and consequence [81]. Therefore, across the ageing literature, multimorbidity (MM) is gaining attention. Its definition varies but is most often described as the presence of two or more comorbidities [82,83], though broader definitions including biopsychosocial and somatic risk factors exist [84].

A population based cross-sectional study in Scotland demonstrated that of the 1,751,841 (presumed HIV-negative) individuals included, 23% had MM overall. This increased with age (64.9% 65-84 years, 81.5% ≥85), social deprivation and presence of a mental health diagnosis [85]. MM is common amongst PLWH particularly at older ages [72,73,81,86,87], with a UK based cross-sectional study of 299 service users aged ≥50 showing at least one comorbidity in 84% and MM in 61% [88]. Guaraldi et al. examined MM in the context of ageing rather than using age cut-off in attendees of the Modena HIV metabolic clinic, defining groups as HIV-ageing (younger seroconversion, longer HIV duration at ≥20.6 years) and HIV-aged (older at seroconversion, shorter HIV duration at <11.3 years). When they compared these groups to age and gender matched population controls MM was significantly higher in those with HIV compared to those without, with highest risk for those in the HIV-ageing group (OR = 5.0, 95% CI 3.3–7.6) than the HIV-aged (OR = 3.8, 95% CI 2.5–6.0), suggesting that duration of HIV is important alongside chronological age [89].

These issues are important as individual comorbidities and particularly MM are associated with increased non-antiretroviral prescriptions and polypharmacy (defined as ≥5 regular medications) [71,72,90,91], as well as healthcare service utilisation [88]. Co-medications and polypharmacy in particular, increases the likelihood of drug-drug interactions (DDI), which have both been demonstrated to be higher in older compared to younger PLWH [91–93]. DDIs may place individuals

at risk of drug toxicities and/or ART failure with the consequent risk of viral replication and resistance.

1.6 HIV and broader age-related problems

Older adults are complex with multiple interacting factors including an ageing physiology, medical comorbidities, polypharmacy and cognitive decline that challenge physical functioning. Declines in functional ability have been demonstrated in older adults with HIV [4,94–96], as have falls [97,98] and frailty [10,11] which may be seen as markers of wider systems failure. Greene et al. explored the concept of 'geriatric syndromes' in PLWH, encompassing multifactorial conditions commonly seen at older ages, such as falls, incontinence, mobility impairment and disability of activities of daily living (ADL). In their cohort of individuals virally suppressed on cART with median age 57, over half (53.6%) had evidence of at least two geriatric syndromes, with number of comorbidities and nadir CD4, but importantly not age, predicting their occurrence [4]. These studies identify that syndromes of ageing are occurring in PLWH at younger ages than might be seen in the uninfected population. This has also been demonstrated in middle age in other vulnerable groups like the homeless [99] and those ageing with other long term problems such as diabetes [100].

Research into functional impairment in those ageing with HIV represents a gap in the literature [81], where interdisciplinary research utilising a disability and rehabilitation framework has been advocated [101]. ADL impairment may also correspond to an unmet clinical need with one study reporting that despite high levels of functional impairment, access to support for instrumental and emotional needs was often lacking [102]. Issues around ageing, illness-related uncertainty and anticipated future care needs are highly important for older adults living with HIV [7,103], particularly those 'survivors' of the pre-cART era who did not expect to see old age [104].

1.7 Frailty

Frailty describes a state of vulnerability to external stressors conferred through negative alterations in multiple physiological systems that occur usually as a product of ageing. Frail individuals can be said to have reached a threshold of physical and cognitive functioning, which may be easily crossed when even minor

stressors are introduced including infection, constipation or a general anaesthetic. This can result in disproportionate changes in functional status that may present as new immobility, falls and/or confusion, which are familiar to those working in geriatric medicine [105].

Frailty is widely recognised as a concept and clinical entity but is hampered by a lack of consensus definition despite international attempts seeking to gain resolution [106–109]. Frailty is therefore described variably leading to heterogeneity in research studies. Two main theoretical concepts have led the way in frailty research, which consider frailty as either a syndrome based on a phenotype [9] or a state of deficit accumulation as assessed using a frailty index (FI) [110]. These are described below and summarised in Table 1.1.

1.7.1 The Frailty Syndrome

Fried et al. used data from the Cardiovascular Health Study to conceptualise a formalised frailty phenotype (FP) based on the presence of five criteria (weight loss, weakness, exhaustion, slowed walking speed and low physical activity) that mark underlying multisystem dysfunction. An individual is frail when they possess a critical mass of these characteristics, measured as three of the five criteria. Those with one or two are 'pre-frail' and those without deficit are considered robust [9]. Using the frailty phenotype they reported that baseline frailty status could predict adverse clinical outcomes such as falls, worsening mobility, increased disability with ADLs, hospitalisation and death [9]. However, this model has been criticised. Firstly it may be difficult to apply in clinical practice due to the inclusion of measured grip strength and timed walk [111]. Secondly and more importantly, it is often described as unidimensional, focussing too heavily on physical characteristics and sarcopenia, which is a reduction in muscle mass and function, whilst neglecting mood, cognition and social indices which are felt to contribute to frailty [105,112]. De Vries et al. go further in suggesting that there are eight (risk) factors central to the concept of frailty across physical (nutritional status, physical activity, mobility, strength and energy), psychological (mood and cognition) and social (social networks) dimensions [109]. Despite these criticisms, Fried's phenotype does allow for a degree of standardisation in measurement and is the most widely evaluated and utilised model in population frailty research [113] with

one systematic review describing that 69% of 150 included studies reported on the frailty phenotype [114].

1.7.4 HIV and frailty

Though the literature is small, frailty has been examined in HIV-positive cohorts in several studies. The majority have utilised the frailty phenotype of a variant thereof, with others describing frailty using a FI, body composition, functional scores or biomarker based indices [11]. The prevalence and predictors of frailty as defined by the FP have been summarised in a systematic review [10], which is presented in chapter 2 of this thesis, with commentary on frailty as assessed by alternative methods.

1.7.2 The Frailty State

The alternative frailty 'state' model comes from Rockwood and Mitnitski's work on the Canadian Study of Health and Aging. They utilise a multi-dimensional frailty index approach in which one accumulates deficits (disease states, symptoms, physical signs or clinical indicators) across a range of functional, physical and cognitive domains with age [110]. A greater number of deficits confers greater degrees of frailty, with a score of around 0.25 (for example representing 10 of 40 deficits) frequently taken as the threshold for frailty [115]. Frailty indices tend to be cohort specific but comparability has been seen if index design is in line with the original concept [116]. This method is thought preferable as it generates a continuous score that can be followed over time or intervention, allowing the dynamic nature of frailty to be assessed [111]. It also allows consideration of biological versus chronological ageing, where one might be deemed fit- of frail-for age, which has shown to better predict outcomes than number of years lived [117]. Lastly it may be preferable as it includes factors across biological, psychological and social domains [109]. However, frailty indices are cohort specific and the large number of variables needed to operationalise the FI can make their use cumbersome in clinical practice, though this has been offset by attempts to embed them within routine electronic clinical databases, such as the computer software packages used in UK general practice [118].

Despite their different approaches in measuring frailty, statistical convergence has been demonstrated between the phenotype and index which strengthens

frailty as an overriding concept [119]. Recently we have seen the first application of a frailty index in the context of HIV [120]. Many alternative frailty screening tools have been developed, with one systematic review identifying 67 frailty instruments, of which only nine were highly cited [113]. These include the wholly self-reported FRAIL model [106] and the SHARE-index which has been applied to European middle-aged adults [121].

Table 1.1: A comparison of the frailty phenotype and frailty index.

Frailty phenotype	Frailty Index
Predefined set criteria	Variable criteria, cohort specific
Criteria based on signs and symptoms	Criteria drawn from comorbidities, functional ability, clinical evaluation
Criteria focus mainly on pre-disability and muscle loss (sarcopenia)	Multi-dimensional criteria
No inclusion of psychosocial/cognitive markers	Potential to include psychosocial/cognitive markers
Assessment can be limited to frailty criteria	Usually requires comprehensive clinical evaluation to complete the index
Categorical variable	Continuous variable
Predetermined frailty/prefrailty cut-offs	Variability in score equating to frailty
Predicts adverse outcomes	Predicts adverse outcomes

1.7.3 Frailty in practice

Frailty is important as it is common and associated with adverse outcomes [105]. Prevalence is dependent upon the method of assessment and can vary widely as demonstrated by a 2012 systematic review including 15 studies of community-dwelling adults aged 65 and over (n=44,894) which showed a frailty prevalence of 4.0-59.1% using all tools and 9.9% when restricted to the FP [122]. The original US Cardiovascular Health Study of community-dwelling adults aged ≥65 had a prevalence of 6.9% [9]. In the UK, the Hertfordshire cohort study of 642 adults aged 65-74 demonstrated a prevalence of 4.1% in men and 8.0% in women [123], with similar prevalence was seen in the 5450 individuals aged over 60 in the English

Longitudinal Study of Ageing, where 14% were frail overall, 6.5% in those 60-69 increasing to 65% in those over 90 [124].

Though frailty has been demonstrated to increase with age across the literature it can still be identified at younger ages. Rockwood and colleagues applied a FI across the life-course (ages 15-102), showing a frailty prevalence of 2% in those under 30 increasing to 22.4% in those ≥65, with mortality predicted by frailty at all ages [125]. The Study of Health, Aging and Retirement in Europe (SHARE) investigated a younger cohort (50-64), in 10 continental countries showing a prevalence of 4.1%, which increased to 17.1% in those ≥65 [126]. This suggests that ageing trajectories vary between individuals. This is supported by work in Dunedin, New Zealand, demonstrating the disparity between chronological and biological age, where for a common current age of 38 years calculated biological age ranged from 29-62 (mean 38, sd 3.23); with biological age being associated with worse function, cognition and self-reported health [127]. As such, frailty is receiving increased attention in non-traditional non-aged settings, particularly where premature ageing is suspected or early presentation of age-related problems are being observed such as survivors of childhood cancer [128], recipients of bone marrow transplants [129] and younger users of intensive care [130].

Irrespective of assessment method, frailty predicts adverse outcomes in terms of falls [9,131], functional decline[132,133], institutionalisation[134,135], hospitalisation with prolonged length of stay [9] and mortality [132,136,137]. That being said, frailty is not an inevitable part of ageing and though the trajectory of frailty for most individuals is from lesser to more frail states, it is a dynamic process [138,139]. There is no cure for frailty but there may be components amenable to treatment or optimisation [105]. Given that on a population level frailty is incurable, progressive and associated with adverse outcomes and reduced quality of life, there are calls for it to be recognised as a long-term condition in its own right [140].

1.8 Pathogenesis of age-related issues in HIV

Ageing has been defined as a ‘progressive, generalised impairment of function resulting in an increasing vulnerability to environmental challenge and a growing risk of disease and death’ [141]. Genetic, epigenetic, environmental and lifestyle factors interact to drive molecular and cellular damage that accumulates when

not repaired. Aged cells may die via apoptotic programmed cell death, which can lead to tissue and broader organ dysfunction or they may enter a non-dividing but metabolically active state of cellular senescence [141]. In addition to these factors, in PLWH, it is important to consider the role of the viral replication, cART toxicities, hepatitis coinfection and the observed disparity in behavioural risk factor exposures, such as alcohol, smoking and recreational drug use as compared to HIV-negative cohorts [74,142]. Ageing is however heterogeneous, being influenced by different environmental exposures balanced against individual biological resilience.

1.8.1 The ageing immune system and the role of inflammation

Natural ageing of the immune system creates an aged immune phenotype that is summarised in Table 1.2. This mirrors that seen in PLWH but at ages much younger than those without [14,143,144]. The starkest effects of ageing are seen in the T-cell lineage with increased T-cell activation, reduced T-cell renewal and naïve T-cell availability, and lower CD4 to CD8 ratio. These ultimately limit replicative ability in the face of antigenic challenge. Both CD4/CD8 T-cell subtypes are driven to terminal differentiation, whereby expression of CD28 cell surface protein is lost and CD57 gained, resulting in loss of survival signalling to local T-cells and impairment of T-cell-B-cell interaction and activation. CD28-negative cells are said to have entered cellular senescence, accompanied by a 'senescence-associated secretory phenotype' in which pro-inflammatory cytokines are released, causing inflammation and further perpetuating T-cell activation [145,146].

Table 1.2: Age-related alterations to the immune system

Ageing immune phenotype
Increased T-cell activation
Decreased T-cell renewal
Decreased pool of naïve T-cells
Lower CD4:CD8 ratio
Terminal differentiation of CD4 and CD8 T-cells
Impaired T-cell-B-cell interaction
T-cell senescence with pro-inflammatory cytokine secretion

HIV induces chronic immune activation via direct T-cell infection and ongoing viral replication that may be exacerbated by the presence of viral coinfection such as hepatitis C (HCV) or reactivation of latent viruses, of which the cytomegalovirus (CMV) has received most attention [8,147,148]. Additionally, HIV is known to impair the integrity of mucosal surfaces, particularly in the gut, creating a 'leaky' mucosa through which microbial products such as lipopolysaccharide (LPS) can pass into the systemic circulation [149]. These products continuously stimulate the innate immune system with activation of monocytes, macrophages and dendritic cells. The combined effect of T-cell activation, ensuing T-cell senescence and stimulation of the innate immune system are to create an excess of pro-inflammatory cytokines that further drive molecular and cellular damage, creating a positive feedback loop whilst driving end-organ dysfunction and comorbid inflammatory diseases [150]. This process has been termed 'inflammaging' and is a prominent theory in the development of age-related comorbidities in those with and without HIV [151,152].

Evidence for inflammation has been demonstrated in those with HIV, with many studies reporting elevations in inflammatory cytokines and markers such as interleukin-6 (IL-6), tumour necrosis factor (TNF) and highly sensitive C-reactive protein (hsCRP), the marker of innate immune activation soluble CD14 and d-dimer, a marker of coagulation [150,153,154]; as well as a number of other biomarkers [155]. These, in particular IL-6, have been shown to be higher at more advanced immunosuppression [156,157], at older ages, and in the presence of other comorbidities [157]. cART has been shown to reduce but not fully reverse inflammation [150] and withdrawal of cART has been shown to increase levels [153]. Markers of inflammation and broader organ dysfunction predict mortality [153] and functional decline [158]. Inflammation has been linked to frailty in those with [159,160] and without HIV [161,162].

1.8.2 Accelerated versus accentuated ageing in HIV

There is considerable discussion around the issue of premature ageing in HIV. There has been debate as to whether HIV represents a model of accelerated or accentuated ageing [163]. In accelerated ageing we observe events/comorbidities

occurring earlier than would be anticipated in the life course, which one might attribute to HIV. Accentuated ageing however is where the occurrence of an event is age-appropriate but more prevalent than compared to an HIV-negative cohort, where HIV may be considered an additional risk factor to those traditionally associated with the outcome of interest [163]. Figure 1.2 illustrates these concepts using the hypothetical example of cancer in those with HIV. In all likelihood it is probably a combination of the two depending upon the body system or disease being considered [163,164]. The immune system could be seen to be ageing at an accelerated rate as described but it is unknown if HIV induces this directly or whether it is due to a distinct process running parallel to 'normal ageing' [150]. This could also be said of frailty [165,166]. However, when looking at specific comorbidities, a large study from VACS demonstrated that incident MI, end-stage renal disease and non-AIDS defining cancers (NADC) occurred at a higher rate, but not earlier age when compared to demographic and behaviourally matched control group, supporting accentuated over accelerated ageing with respect to these comorbidities [167].

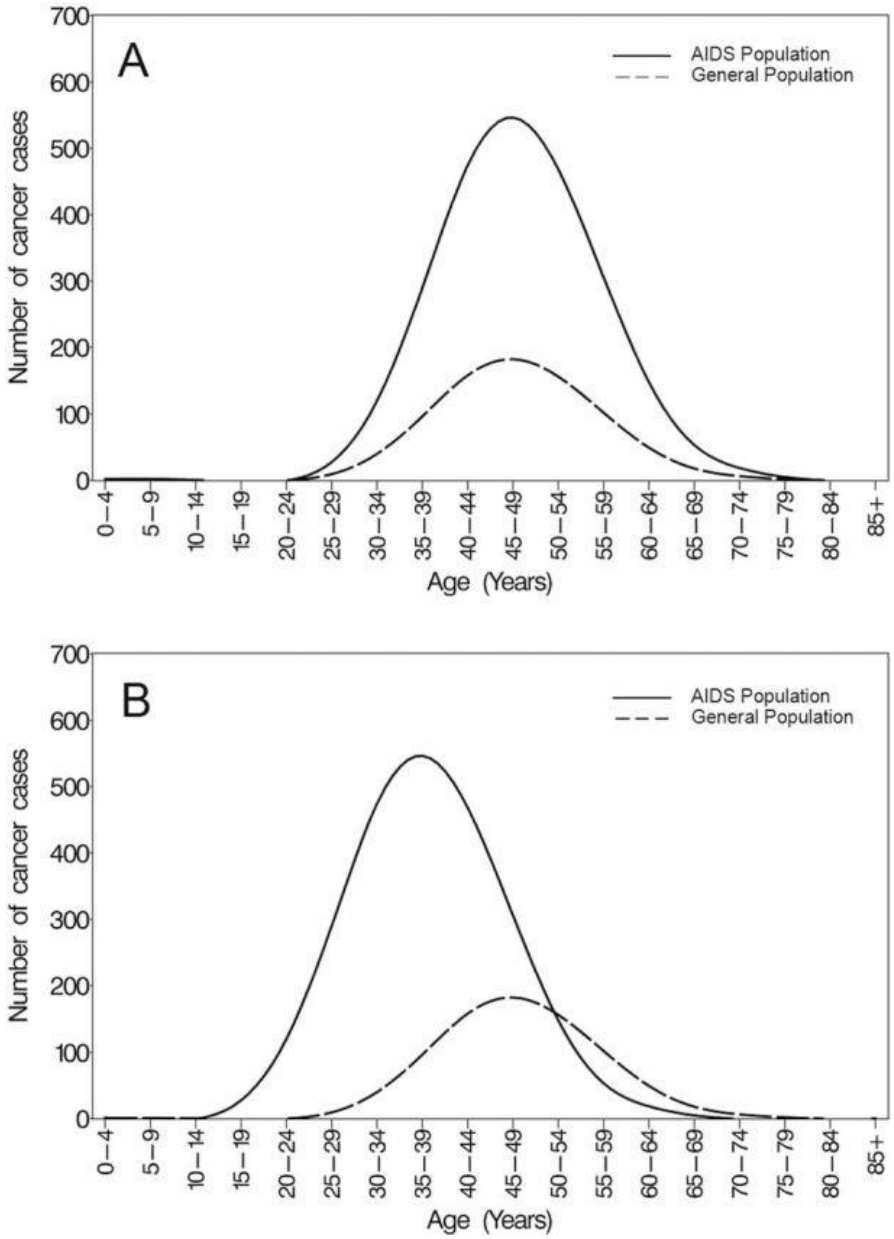


Figure 1.2: Hypothetical age-at-diagnosis distributions of cancer in the AIDS and general populations. (A) Accentuated: cancer occurs at the same ages but more often among HIV-infected participants than among HIV-uninfected comparators. (B) Accelerated and accentuated: cancer occurs earlier among HIV-infected participants compared with HIV-uninfected comparators and there are more cancer events. Reprinted from Pathai et al. [163] with permission

Caution should be taken in defining premature or accelerated ageing in PLWH as there may be many biases at play. Individuals with HIV are often well-linked to healthcare services and as such comorbid disease may be screened for and identified differentially than in those without HIV, leading to ascertainment bias [168]. Additionally, in the case of proactive screening, earlier identification may result in lead-time bias when compared to routine or symptom driven screening

practices employed in the general population. As previously mentioned the control group utilised within a study may limit the conclusions that can be inferred for a number of reasons [169]. Where population or registry controls are sampled, you may see variance in age distribution between those with and without HIV with underrepresentation of PLWH in the highest age groups, particularly in those over 65 where we would anticipate age-related disease to be more prevalent, thus missing these cases and skewing age of disease onset to younger ages. This was demonstrated in a study utilising US registry data to assess age at cancer diagnosis in those with AIDS, where after adjustment for population structure there was no or minimal difference in age of onset in most cancer types [170]. Additionally, groups may not be balanced in terms of known disease risk factors, or this data may be lacking resulting in residual confounding and potential for false or overestimated attribution to HIV. Returning to the above study, after standardisation for age distribution only lung and anal cancers occurred at a significantly younger age in those with AIDS; however information on risk factors of smoking and oncogenic viruses, as well as knowledge of anal screening processes that could account for these findings were lacking [170].

1.9 Summary

The HIV-positive cohort is ageing with evidence that age may negatively influence the natural history of HIV, particularly in the setting of newly diagnosed individuals where late diagnosis is prevalent. Additionally, though still contentious, HIV may affect the natural ageing process, possibly though driving excess systemic inflammation.

We know that the HIV-positive population is diverse and that some individuals may experience negative ageing in the form of excess comorbidity and functional decline. The sheer numbers of older adults living with HIV coupled with the potential adverse outcomes make this a subject of clinical and research importance recognised by leading research, policy and patient advocacy groups such as the UK Government House of Lords [171], the Terrence Higgins Trust [7] and US National Institute for Health, who promote the involvement of geriatricians and the use of gerontological research methodologies [8]

Therefore, there is a need and an appetite for exploration of these issues and a move towards the provision of services dedicated to older adults living with HIV. HIV has drifted into territory familiar to geriatricians with issues of MM existing alongside functional and psychosocial disadvantage. HIV needs to be viewed through a lens of systems ageing, which can be characterised by the presence of frailty. Frailty may ultimately represent a means of identifying individuals at risk of negative ageing within this heterogeneous population that may need enhanced services as they age with HIV.

1.10 Study Aims

Some of the problems facing individuals ageing in the presence of HIV have been outlined in this chapter. There is inherent complexity in this cohort given the interacting forces of their underlying HIV and its associated cART, the presence of NICM and age-related functional decline, all of which cannot be isolated from the psychosocial circumstances in which they live. Frailty in its broadest description allows us to draw from all the above to identify those at risk of a negative ageing trajectory. At the conception of this study frailty research in HIV was in its infancy with no European cohorts reported upon, and a failure to concentrate specifically on the older HIV-infected population.

Studies have used Fried's phenotype as the main marker of frailty but its application has varied between studies as demonstrated in chapter 2. However, it remains a single, unidimensional model of frailty with no published work including a comprehensive multi-dimensional assessment, akin to a comprehensive geriatric assessment, which is the gold standard in geriatric medicine [105]. This would include objective markers of cognition, depression, body composition, muscle mass and strength, alongside socio-economic, functional, quality of life and biological (including HIV) factors, which may all contribute to a frailty state. Therefore, there may be a role for frailty assessment in clinical HIV practice. As such, to meet the needs of this evolving population, we must first describe the condition accurately, providing an idea of the magnitude of frailty (prevalence), and pre-frailty, alongside the issues of sarcopenia, neuro-cognitive and functional impairment. The unique population demographics in Brighton and

the South East enabled us to study a cohort of HIV infected patients with an age range extending beyond 80 years.

1.10.1 Primary aim

The primary aim of this study is to utilise the Fried frailty phenotype model to establish the prevalence of frailty in a cohort of HIV-infected individuals aged 50 or more living in the South East of England. Additionally, we aim to assess the relationship between frailty status and a range of biopsychosocial factors including socio-demographics, behavioural risk factors, psychological and social resources, body composition and health status inclusive of comorbidities and HIV parameters. From this we aim to utilise logistic regression techniques to examine potential predictive or protective factors for frailty within this older HIV-positive cohort.

All participants will be drawn from National Health Service (NHS) provided HIV-clinics and therefore will be in receipt of universal free healthcare, which may positively influence treatment experience. Using this assumption, we estimate an anticipated frailty prevalence of around 10% for this cohort, which is at the lower end of the published literature available at the time of project conception (9-19%).

We hypothesise that frail individuals will demonstrate more negative profiles regarding sociodemographic, comorbid, HIV and psychosocial factors than non-frail counterparts. We anticipate that this cohort will be (cART) treatment experienced and as such hypothesise that non-HIV factors will be stronger predictors of frailty than HIV-factors.

1.10.2 Secondary aims

- To undertake a systematic review of frailty prevalence and predictors in individuals with HIV utilising the existing research literature to inform the data analysis strategy.
- To investigate the presence of sarcopenia in a sample of the cohort and assess the association between sarcopenia and frailty status.
- To examine the association between frailty status and potential biological predictors of nutrition, physical activity and inflammation.

- To examine the association between frailty status and psychological functioning, including cognition, well-being, motivation, mood, social interaction and quality of life.

Chapter 2 - Systematic review of prevalence and predictors of frailty in individuals with HIV

2.1 Introduction

Longer survival with modern combined antiretroviral therapy (cART) alongside greater incidence of late-life acquisition of the human immunodeficiency virus (HIV) is driving an increase in the age of the HIV-positive (HIV+) cohort. HIV in older adults presents a number of challenges, including comorbidities not traditionally associated with HIV infection [71], including falls [97], functional impairment [95], and frailty [172], which are more common in older adults. Whether HIV itself or treatment toxicities cause premature or accelerated aging is subject to ongoing debate [163,168] and is considered a research priority [8].

With an increasing number of older adults receiving HIV care, services will need to be adapted to meet their complex needs. In general, chronological age may not be the best predictor of prognosis or individual need [173]. A more-useful model for risk stratification may be the presence or absence of frailty. Frailty describes a state of vulnerability to stressor events resulting from declines in multiple physiological systems. When present, frailty is associated with adverse outcomes including falls, hospital admission, and death [9,105,137]. The difficulty in using frailty as a concept is the lack of consensus definition, particularly regarding how it should be measured [107]. The most widely used model in HIV+ and HIV- populations is the frailty phenotype (FP) [114] characterized by Fried and colleagues [9]. The FP comprises five criteria (weight loss, exhaustion, low physical activity, weak grip strength, slow walking speed), with frailty defined by the presence of three or more criteria. Those with one or two are classed as prefrail and with none as robust [9].

There is heterogeneity in HIV frailty research, with different authors using various measures and definitions of frailty, making it difficult to quantify the burden of frailty fully in the context of HIV. The objective of the chapter was therefore to conduct a systematic review of the original literature pertaining to frailty prevalence and predictors in individuals with HIV using the FP as a standard model. The systematic review presented in this chapter has been published in

the Journal of the American Geriatrics Society with the manuscript included in Appendix 1.

2.2 Methods

2.2.1 Search Strategy

The goal was to identify observational studies assessing frailty status in individuals with HIV. A systematic electronic search was conducted using Medline, CINAHL, EMBASE, PsychInfo, and PubMed, which were searched from January 2000 to April 2014 using database-appropriate medical subject headings alongside “HIV,” “human immunodeficiency virus,” “acquired immunodeficiency syndrome” combined with “frail*,” “reduced functional reserve,” “functional impairment,” “reduced physiological reserve,” and “physiological vulnerability.” Broad “function” terms were used to capture studies in which frailty was part of a wider functional assessment. International HIV and acquired immunodeficiency syndrome (AIDS) conference abstracts, major HIV and gerontology journals were also searched. Reference lists of relevant review articles and articles reviewed at full-text stage were screened by hand.

2.2.2 Eligibility Criteria

The following inclusion criteria were applied in article selection: original observational research presented; frailty defined using the Fried FP, or modified variant thereof, to allow standardization (therefore excluding studies published before its description in 2001); inclusion of data on HIV+ adults; and frailty prevalence for individuals with HIV stated, easily calculable, or obtainable from authors. Studies not meeting the above criteria were excluded. Although language was not an exclusion criterion or limit set during searches, all citations found were in English.

2.2.3 Study selection

Two reviewers, Tom Levett (TL) and Fiona Cresswell (FC), independently conducted selection for full-text review by applying eligibility criteria to titles and abstracts. Articles deemed relevant or for which further clarification was required were retrieved for full text review. Authors were contacted when points of clarification were needed [174–176]. The reviewers independently assessed selected

full-text articles, and after discussion and consensus review where needed (by Martin Fisher- MF), a list of studies for inclusion was finalized.

2.2.4 Quality Assessment

Study quality was evaluated with respect to bias using the Newcastle-Ottawa Scale (NOS) [177], a quality assessment tool for nonrandomized studies with scales available for different observational methodologies, which were applied according to study type. Broadly, the NOS criteria evaluate quality in the domains of selection, comparability, and outcome, awarding a designated number of stars to each study in each domain depending on whether quality markers are met. The scale was adapted for cross-sectional studies by reducing the weight allocated to validation of exposure (HIV) and outcome (frailty), to be awarded 1 rather than 2 points, making weighting comparable with that awarded for cohort and case–control scales, preventing artificially high-quality scoring of cross-sectional studies. Given the importance of statistical analysis, scoring for an appropriate approach was substituted into schemes for cohort and case–control study design types.

2.2.5 Data Extraction

Two of the authors (TL, FC) designed a data extraction form and independently applied it to each study. Data were extracted on study design, population characteristics, frailty definition and frailty prevalence (for HIV+ and HIV- where control groups were included), and significant frailty predictors. Data that each reviewer extracted were compared for consistency, and any disagreements were resolved by consensus or a third reviewer (MF).

2.2.6 Statistical Analysis

A meta-analysis of frailty prevalence was planned to generate a summary prevalence with corresponding 95% confidence intervals (CIs). Comprehensive Meta-Analysis software (Englewood, USA) was used. A random-effects meta-analysis of the included studies presenting cross-sectional data was performed [174,178–183], producing summary prevalence of 8.6% (95% CI=6.5–11.3), although heterogeneity was high, with an I^2 score of 77.63, which did not fall to below 75 with sensitivity analysis when additional factors were considered, including country of origin (U.S. vs non-U.S.), ethnicity (white vs black), age (<vs ≥ 50), or

ART use (whole cohort vs <100% use). Given that variability in prevalence is largely due to heterogeneity of the studies, it was decided not to present the findings as a meta-analysis further. Figure 2.1 shows the funnel plot created to assess potential publication bias, which owing to the limited number of studies in the review, could not provide conclusive evidence, although from the observed funnel plot, the spread of studies was more or less symmetrical, suggesting an absence of publication bias.

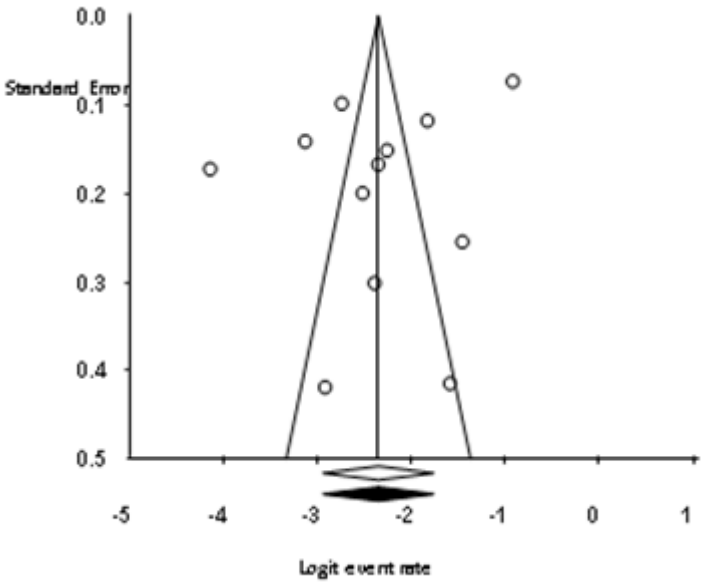


Figure 2.1: A funnel-plot to assess publication bias of included studies (utilizing random effects model).

2.3 Results

2.3.1 Search results and study selection

Literature review found 322 citations: 275 from database searches and 47 from index searching of bibliographies, journals, and conference proceedings. Of these, 103 were duplications, and a further 178 were excluded after title or abstract review because of non-relevance. Forty-one were selected for full-text review, with a further 28 exclusions due to duplicated presentation of data (n=6), lack of frailty assessment (n=12), frailty not defined by FP (n=4), or absence of primary data (n=6). Thirteen studies met full inclusion criteria. Figure 2.2 shows the selection and exclusions.

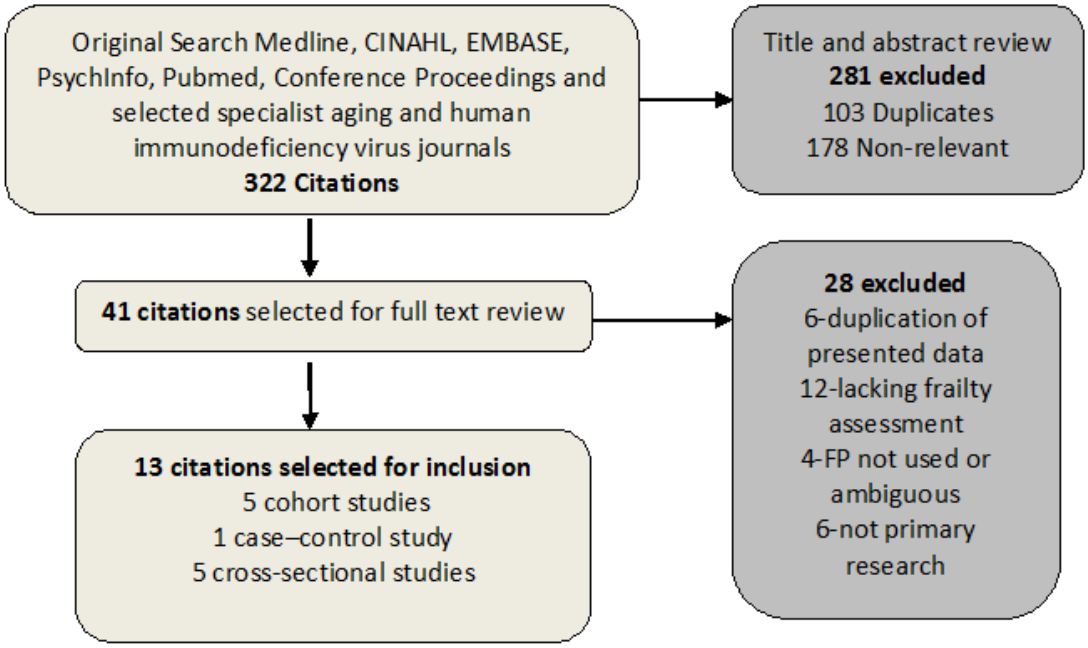


Figure 2.2: Flow diagram of study selection process

2.3.2 Study characteristics

Of the 13 studies selected, five were of cohort design (two prospective, three retrospective) [166,175,176,184,185], with four presenting data from the Multicenter AIDS Cohort Study (MACS) [166,176,184,185]. One study used case–control design,[181] and seven were cross-sectional [178–180,182,183,186] (one nested within a prospective cohort) [174]; 12 were presented in full article format and one as conference abstract. Studies were largely urban community or university clinic based, with only one from a resource-poor setting [181]. Studies varied in size from 41 to 2,150. Eleven studies were U.S. based, with the two remaining studies from Mexico and South Africa. All used a frailty assessment based on FP criteria, with the three retrospective cohort studies using a frailty-related phenotype (FRP) comprised of four rather than five criteria, with grip strength data lacking [166,184,185]. One study measured phenotypic criteria differently from other studies [186]. Table 2.1 shows the general study characteristics and description of frailty parameters for the included studies.

Table 2.1: Characteristics of included studies.

Author, Year (Country)	Design	Population	Age of HIV+ Participants	Male %	Study N	HIV+ N	HIV+ Frailty %	Outcome Measure	Frailty Criteria
Althoff, 2013 (United States)[176]	Cohort	MACS Men who have sex with men, aged ≥18 ± HIV. Urban Oct 2007-Sept 2011	53.8 frail, 50.5 non-frail (median)	100	1,946	898	28.6 (12% pv)[a]	Prospective Modified FP Frail if ≥3/5 criteria	Weakness (grip strength[b]) Slowness (4-m timed walk[b]) Self-reported weight loss Self-reported exhaustion[c] Low physical activity[d]
Desquilbet, 2007 (United States)[166]	Cohort	MACS HIV- cohort Apr 1994-Nov 2004 HIV+ cohort Apr 1994-Jan 1996	39 (median)	100	2,150	245	13.9 (7.2% pv)[a]	Retrospective FRP Frail if ≥3/4 criteria	Self-reported slowness[e] Self-reported Self-reported exhaustion[c] Low physical activity[d]
Desquilbet, 2009 (United States)[184]	Cohort	MACS HIV+ cohort April 1994-April 2005	45 (median)	100	1,046	106	- (5.4% pv)[a]	Retrospective FRP Frail if ≥3/4 criteria	Self-reported slowness[e] Self-reported Self-reported exhaustion[c] Low physical activity[d]
Desquilbet, 2011 (United States)[185]	Cohort	MACS HIV+ cohort initiating ART pre-2001	43 (median)	100	596	596	13.9	Retrospective FRP Frail if ≥3/4 criteria	Self-reported slowness[e] Self-reported Self-reported exhaustion[c] Low physical activity[d]
Erlandson, 2012 (United States)[178]	Cross-sectional	HIV+ aged 45–65 on ART University hospital clinic January 2009-January 2010	50.8 (median)	85	359	359	7.5	Prospective modified FP Low function (frail) if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m walk[g]) Self-reported weight loss Self-reported exhaustion[i] Low physical activity[d]
Greene, 2014 (United States) [183]	Cross-sectional	Community study HIV+ aged 50 on ART	57 (median)	94	155	155	9.0	Prospective FP	Weakness (grip strength[f]) Slowness (4.5-m walk[g]) Self-reported weight loss Self-reported exhaustion[h] Low physical activity[i]

Author, Year (Country)	Design	Population	Age of HIV+ Participants	Male %	Study N	HIV+ N	HIV+ Frailty %	Outcome Measure	Frailty Criteria
Ianas, 2012 (United States) [179]	Cross-sectional	Convenience sample; HIV+ aged ≥18 ± ART University outpatient clinic May-December 2010	21–78 (range)	74	100	100	19.0	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m walk[g]) Self-reported weight loss Self-reported exhaustion[h] Low physical activity[d]
Onen, 2009 (United States)[180]	Cross-sectional	Convenience sample University hospital clinic. HIV+ aged ≥18 ± ART June-Dec 2008	41.7 (mean)	71	445	445	9.0	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m walk[g]) Documented weight loss Self-reported exhaustion[h] Low physical activity[d]
Pathai, 2013 (South Africa) [181]	Case-control	Unselected sample aged >30 HIV+ ± ART Community treatment centre HIV- controls community HIV prevention site May-Dec 2011	41.1 (mean)	27	504	248	19.4	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m walk[g]) Documented weight loss Self-reported exhaustion[h] Low physical activity[d]
Piggott, 2013 (United States)[175]	Cohort	AIDS Linked to IntraVenous Experience History intravenous drug use ± HIV Community-based cohort. From July 2005	48.7 (median)	63	1,230	357	14.6	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m walk[g]) Documented weight loss Self-reported exhaustion[h] Low physical activity[d]

Author, Year (Country)	Design	Population	Age of HIV+ Participants	Male %	Study N	HIV+ N	HIV+ Frailty %	Outcome Measure	Frailty Criteria
Sandkovsky, 2013 (United States) [186]	Cross-sectional	Pilot study Convenience sample University hospital clinic HIV+ aged 20–39 or ≥50 ± ART	20–70 (range)	71	41	41	17.1	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip >1 SDs below mean) Slowness (Timed Gait Test >11 seconds) Self-reported weight loss Exhaustion (Fatigue Severity Scale score >36) Low activity (POMS activity scale <2)
Terzian, 2009 (United States)[174]	Cross-sectional	Nested within Women's Interagency HIV Study Urban, community cohort of women aged ≥14 ± HIV Jan-Dec 2005	41 (median)	0	1,781	1,206	9.0	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength) Slowness (4-m walk time) Self-reported weight loss Self-reported exhaustion[h] Low physical activity[d].
Abstract Davila-De la Llavre, 2013 (Mexico)[182]	Cross-sectional	Community study HIV+ aged ≥50 on ART	54 (mean)	80	116	116	5.0	Prospective FP	Fried phenotype Individual criteria not specified

[a] Frailty prevalence based on percentage of visits at which frailty identified.
[b] Lowest 20% for activity.
[c] Answered "yes" to, "During the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities?"
[d] Answered "yes, limited a lot" to, "Does your health now limit you in vigorous activities?"
[e] Answered "yes, limited a lot" to "Does your health now limit you walking several blocks?"
[f] Predefined cut-offs based on sex and body mass index.
[g] Predefined cut-offs based on sex and height.
[h] Response of 3–4 days per week or most of the time to, "Everything I did was an effort" or "I just could not get going," on the Center for Epidemiologic Studies Depression Scale.
[l] Minnesota Leisure Time activity questionnaire

2.3.3 Quality

Table 2.2 shows study quality as assessed using design-specific NOS demonstrating that of a maximum available 9 points there was a range from 3 to 8, with lower-quality scores assigned to conference abstracts.

Table 2.2: Newcastle-Ottawa Scale quality evaluation according to design type.

First Author, Year	Selection	Comparability	Outcome	Total
Cohort design				
Althoff, 2013 [176]	3	2	3	8
Desquilbet, 2007 [166]	2	2	3	7
Desquilbet, 2009 [184]	2	2	3	7
Desquilbet, 2011 [185]	3	2	2	7
Piggott, 2013 [175]	2	2	2	6
Case–control				
Pathai, 2012 [181]	2	2	3	7
Cross-sectional				
Erlandson, 2012 [178]	2	2	3	7
Greene, 2014 [4]	2	2	2	6
Ianas, 2012 [179]	2	2	3	7
Onen, 2009 [180]	3	0	3	6
Sandkovsky, 2013 [186]	3	1	2	6
Terzian, 2009 [174]	2	2	3	7
Abstracts (cross-sectional)				
Davila-De la Llavre, 2013 [182]	2	0	2	4

2.3.4 Frailty prevalence

Prevalence was measured in two ways. When cross-sectional data were presented, prevalence was provided for individuals and ranged from 5% in the Mexican study [182] to 28.6% in the MACS cohort [176]. In the MACS articles, frailty was assessed on multiple occasions, allowing for prevalence to be calculated using total number of individuals as the denominator (based on at least one visit with frailty), ranging from 13.9% to 28.6%, and using total person visits as the denominator, which resulted in lower prevalence (5.4–12%) [176,184]. Across the

MACS timeline, prevalence of frailty in terms of person-visits decreased from 7.6% in 1994–95 (pre-cART era) to 4.5% in 2000–05 (post-cART era), with increases in median age from 41 to 48 and proportion of those on treatment from 42.3% to 80.2%. In the most-recent evaluation, from 2007 to 2011 (established cART era), with frailty assessed prospectively with the addition of grip strength, prevalence had risen to 12% of visits or 28.6% of individuals with at least one frailty visit, along with further increases in median age to 53.8 and in proportion receiving cART from 80.2% to 84.2%. Data were presented from the AIDS Linked to the IntraVenous Experience (ALIVE) cohort, including HIV+ and HIV- individuals with past or present intravenous drug use, in which FP was present in 12.3% of all participants and 12.4% of person visits. [175] Dividing participants according to HIV status, 14.6% of HIV+ and 11.3% of HIV- were frail (data provided by author).

2.3.5 Predictors of frailty

HIV status

Five studies included HIV- controls. The MACS cohort examined frailty before the introduction of cART [166], when the prevalence of FRP in HIV- participants was 1.5%. In this study, for 1994 to 1996, the odds of expressing FRP, adjusted for age, ethnicity, and education, were almost 11 times as great in HIV+ as in HIV- individuals (adjusted odds ratio (aOR)=10.97, 95% CI=6.37–18.88) when all person-visits were analyzed. The odds were lower, but remained significant, when weight loss, which had a strong association with HIV before cART, was removed as a FRP criterion (OR=4.49, 95% CI=1.98–10.09). With established cART, one study (for MACS) demonstrated significantly higher frailty prevalence in HIV+ (12%) than HIV- men (9%) (p=.002) [176]. Further support for an association with HIV status was provided in the ALIVE cohort, in which HIV was associated with a 66% greater likelihood of frailty (aOR=1.66, 95% CI=1.24–2.21) [175], and in a study from South Africa in which the odds of frailty in those with HIV were more than twice as great (aOR=2.14, 95% CI=1.16–3.92) [181].

Age

In the pre-cART MACS, a 10-year increase in age was associated with a significantly greater risk of frailty (OR=1.61, 95% CI=1.21–2.15), which was lower

but remained significant when AIDS was excluded (OR=1.53, 95% CI=1.11–2.11) [166]. This persisted in the cART era (1996–2005), with a 10-year age increase associated with a greater risk of frailty (OR=1.52, 95% CI=1.24–1.87) [184]. In later MACS data from 2007 to 2011, the proportion of visits at which frailty was demonstrated increased with increasing age [176]. Age was significantly associated with frailty in two additional studies [175,180]. In a South African study, older age was a significant predictor in HIV+ women but not men (OR=2.50, 95% CI=1.35–4.58) in a predominantly female HIV+ cohort (73.1%) [181]. Another study showed no association with age and frailty after controlling for CD4 count, but older age was significantly associated with lower CD4 count, which predicted frailty [179].

Sociodemographic factors

Studies varied in sociodemographic factors presented. In early MACS analysis, before 1996 [166], college education was associated with greater frailty, but after 1996, the converse is seen, with lower educational attainment associated with greater frailty (OR=1.73, 95% CI=1.19–2.50) [184] and conversion to frailty [176]. Some studies [180] support this association between frailty and lower educational achievement but not others. Ethnicity (non-Hispanic black) was associated with frailty in the MACS cohort only after 1996 [176,184]. Unemployment and low annual income were significantly associated with frailty in two studies [178,180] but not reported elsewhere.

Comorbid conditions

The recording and handling of comorbidities varied between studies, with no standardized list used. Comorbidities were ascertained from a combination of self-report, laboratory parameters, and clinical notes review. Studies reported on specific comorbidities or comorbidity counts [175,178–181]. In studies in which comorbidities were examined, individuals with HIV who were frail had significantly more comorbidities than those who were robust [175,176,178,180]. The most consistently replicated comorbidities included psychiatric disease, particularly moderate to severe depression [176,178,180,184]; cognitive impairment using the International HIV Dementia Scale [180]; chronic kidney disease [176,180]; diabetes mellitus [176]; and low body mass index [180,181]. Hepatitis C co-infection was

associated with frailty in only one study and was restricted to those aged 50 and older [179].

HIV factors

CD4 cell count

Low CD4 count was the most consistently reported HIV factor associated with frailty, with current CD4 [166,174–176,178,181,184] more predictive than nadir count, which showed significant association in only one study [180]. In MACS, median CD4 count increased over the duration of the study, with a corresponding drop in frailty prevalence overall, although the risk of frailty increased as CD4 fell (CD4 count 100 cells/mm^3: aOR=2.80, 95% CI=1.97–3.98; CD4 count 200 cells/mm^3: aOR=1.98, 95% CI=1.57–2.50; CD4 count 350 cells/mm^3: aOR=1.36, 95% CI=1.22–1.50) [184]. This CD4 relationship was also observed in one cross-sectional study, with frailty prevalence of 43.5% for CD4 of less than 200 cells/mm^3, 19.2% for 200 to 350 cells/mm^3, and 7.8% for more than 350 cells/mm^3 [179]. A high CD4 count was protective of frailty in one study, with a CD4 count of greater than 750 cells/mm^3 associated with OR=0.66 (95% CI=0.57–076) [184]. CD4 count remained a strong predictor of frailty even in individuals with viral suppression and when AIDS and comorbidities such as tuberculosis and hepatitis C were controlled for [181,184].

Viral load

Viral load (VL) is not as strongly associated with frailty as CD4 count, with positive association observed only in pre-cART MACS, with the odds of those with a VL of more than 50,000 copies/mL having FRP being almost three times as great (OR=2.91, 95% CI=1.08–7.85) as that of those without [166]. Frailty remained more common in those with a VL of more than 50,000 in the post-cART era but not significantly so after adjusting for CD4 count [184]. Other studies report no significant association with peak or current VL or virological failure on treatment [175,178,179,181].

AIDS

When the relationship between AIDS (not including CD4<200 cells/mm^3) and frailty was examined, all but one study [178] showed the risk of frailty to be higher in those with AIDS. In MACS, risk was lower after the introduction of cART (before

cART: OR = 9.89, 95% CI=4.70–20.80; after cART: OR=3.34, 95% CI=2.24–4.94) [184]. This association was less evident in a study of women, in which the greater risk of frailty was seen only in univariate (OR=1.55, 95% CI=1.03–2.34) and not multivariate analysis; when AIDS was excluded, frailty prevalence in those with HIV was 7%, compared with 8% in HIV- controls [174]. Lastly, individuals with AIDS were more likely to become frail than those without (OR=1.57, 95% CI=1.06–2.34) [176].

2.4 Discussion

This systematic review found multiple studies that all demonstrated frailty in individuals with HIV. Frailty prevalence ranged from 5.0% to 28.6% depending on the cohort studied. Frailty in these studies was associated with older age but was present at younger ages not traditionally associated with frailty, which is mainly seen as a syndrome of old age. HIV increased the likelihood of developing frailty, and in individuals with HIV, older age, comorbidities, AIDS diagnosis, and low current and possibly nadir CD4 cell count were predictors of frailty.

To the knowledge of the authors, this is the first evaluation of frailty in individuals with HIV using systematic review methodology. The strengths of this study include a comprehensive search strategy encompassing multiple electronic databases alongside conference proceedings and target journals to capture all the published literature. In addition, the focus on frailty assessment based upon the Fried FP attempted standardization across the studies. Although heterogeneity was still considerable, inclusion of alternative frailty assessment methods would have increased heterogeneity. Despite recent international attempts, there is still no consensus definition of frailty [107,108] although the FP is the most commonly used tool in population-based studies [114].

To contextualize the prevalence of frailty in individuals with HIV, studies in HIV-populations using the FP in community-dwelling adults aged 65 and older include the U.S. Cardiovascular Health Study, in which the prevalence was 6.9% [9], and a 2012 systematic review of 15 studies (n=44,894), in which the prevalence was 9.9% [122]. The Study of Health, Aging and Retirement in Europe, which investigated a younger cohort, found prevalence of 4.1% in those aged 50-64, which increased to 17.1% in those aged 65 and older [126]. Therefore, the

prevalence seen in the broadly younger HIV+ population, with highest median age of 57, is comparable with that of cohorts of HIV- individuals aged 65 and older.

There are some limitations to this review. First, despite a thorough search strategy, some articles may have been missed. This would be important if these contradicted the results presented here, but given the global finding of frailty occurrence and chiefly consistent associated factors, it is likely that the effect would be small. Second, the large amount of heterogeneity across the studies in terms of the populations studied and the interpretation of the FP make comparisons difficult. Third, transitions between frailty states were not evaluable in the cross-sectional studies and where measured in longitudinal studies, showed movement in and out of frailty, which makes defining its occurrence difficult. Last, some of the data presented come from the era before effective cART and so may not reflect the current largely well-treated cohort who may have a different aging trajectory from that of those diagnosed before its availability.

Heterogeneity was seen across the study populations, particularly with reference to the longitudinal cohorts, which focus on particular populations, including men who have sex with men (MSM) in MACS [166,176], intravenous drug use in ALIVE [175], and women in the women's interagency health study [174]. Most studies originated from the United States, suggesting a need to explore geographical differences in frailty and the many potential confounders such as nutrition, late versus early diagnosis, HIV duration, and ART experience. Most studies used convenience over random sampling strategies, making it difficult to determine the role of selection bias and confounding. Furthermore, most recruited through HIV clinics. Clinic attendees may represent the less-healthy end of the spectrum of service users and bias the study toward overestimation of frailty; conversely, individuals at the fitter end of the cohort may be more able to attend or be more proactive about their own health, leading to underestimation.

Regarding the interpretation of the FP, the clear majority used a FRP based on retrospective data or a modified FP, none of which, including the original phenotype, have been validated in younger HIV+ cohorts, which may affect the accuracy of frailty diagnosis with potential for misclassification. In MACS

particularly, frailty may have been underestimated when four rather than five criteria were used, because a trend of reducing frailty prevalence was reversed with the addition of grip strength in 2005 [176]. Despite this lack of validation, when the predictive ability of the phenotype in terms of adverse outcomes was examined, it appeared consistent with that of traditional elderly cohorts aged over 65 years [175,180,185]. Using population-based cut-offs for phenotypic criteria has been shown to correlate well with original methodology [187].

A question remains as to whether there is equivalence between frailty in younger HIV+ individuals and older HIV- individuals. There are some similarities in that prevalence appears to increase with age and pathophysiological mechanisms may overlap. Recent attention has fallen on the role of inflammation as a driver of or trigger for frailty states through multisystem degradation [105,188]. Inflammatory profiles appear similar in those with and without HIV [160,162]. Early immune insult and sustained pro-inflammatory environment may trigger the premature occurrence of frailty in HIV, which could explain why current immune dysfunction, evidenced by lower CD4 cell counts, is demonstrated as a consistent predictor of frailty in HIV.

The FP is criticized for using a one-dimensional approach to frailty that focuses too heavily on physical characteristics [112], which in a HIV context may disproportionately represent those with lipodystrophy secondary to certain ART, although this and other markers of body composition and sarcopenia have not been widely explored as explanatory factors. Self-reported surrogate markers of exhaustion and low physical activity may also be over-reported in individuals with additional comorbid conditions, particularly depression, which may be a confounding factor. It cannot be said that frailty is associated with the same negative outcomes of frailty as seen in older adults because longitudinal work reporting this is limited.

Before making any recommendations regarding routine assessment and treatment of frailty in individuals with HIV, alternative explanations, particularly the role of unrecognized depression, need to be considered. Given the link between immune dysfunction and low CD4+, it may be reasonable to investigate the role of ART in ameliorating frailty in those naïve to treatment or with poor

adherence, particularly in light of results of the Strategic Timing of Antiretroviral Treatment trial, which promotes early initiation of ART, avoiding low CD4 counts [51]. This should accompany wider public health approaches to proactive testing to avoid late diagnosis and advanced immunosuppression. Given the potential adverse outcomes associated with frailty, certain predictors may prompt targeted frailty assessment and, where found, trigger intervention, which should revolve around multidisciplinary comprehensive geriatric assessment. It would seem a reasonable approach to recommend positive lifestyle interventions, particularly exercise, which may have wider-reaching benefits for the cohort.

This review highlights the question of frailty in individuals with HIV, which appears to have prevalence comparable with that of HIV- individuals aged 65 and older. Important predictors include older age, advanced immunosuppression, and comorbidities. There is an ongoing need for further research in the form of well-designed longitudinal cohort studies conducted across the lifespan in mixed populations that reflect the current cohort aging with HIV. Given the implications, the inclusion of frailty measures in established HIV longitudinal studies should continue, representing a vital source of information on incidence, pathophysiology, predictors of transition to higher frailty states, and outcomes of prefrailty and frailty. Although achieving a representative HIV- control group is challenging, studies with well-chosen controls will help to confirm any contribution of HIV in addition to other disease and sociodemographic factors to frailty. This and longitudinal work focusing on whether frailty in individuals with HIV is associated with the same adverse outcomes seen in HIV- individuals could promote clinical and research activity into prevention and reversal of frailty. Ultimately, HIV provides an ideal model to examine aging from mid- to late life, which may provide insights into frailty development in uninfected populations.

2.4.1 Recent applications of the frailty phenotype in HIV

Frailty continues to be assessed in the context of HIV. Subsequent publications and studies not meeting the inclusion criteria for the systematic review are summarised in Table 2.3. New studies that would have met inclusion criteria are outlined below.

Smit et al. present a small cross-sectional sub-study of 50 PLWH aged >45 randomly recruited from the Cardiovascular Assessment Risk Examination study (CARE) in Boston, US. In this cohort with mean age of 57 and 50% females, a modified FP [180] demonstrated frailty prevalence of 16% (8/50) with 44% prefrail and 40% robust. Frail individuals were older, more likely female, less likely to be on cART, had higher functional impairment and were more likely to report food insecurity, which had not been examined elsewhere [189].

A FP method, using lowest quintile based cut-offs for walking speed and grip strength has been employed in the Dutch AGEhIV study. This study reports on 521 individuals aged >45 with HIV and 513 comparable negative controls drawn from users of sexual health services. In this group, frailty was present in 10.6% of those with HIV and 2.7% without, equating to a 65% higher risk of frailty if HIV-positive after adjustment for confounders (OR=1.65 95% CI=1.24-2.20). They assessed predictors in terms of risk of higher frailty states compared to being non-frail, with significant association seen with depressive symptoms, low BMI and higher waist-to-hip ratio (WHR), speculating a role for lipodystrophy. After adjustment, no HIV-factors predicted frailty in those with HIV [190].

Further analysis of frailty has been documented from WIHS. A cross-sectional assessment of frailty and its association using a FP model in women with and without HIV, showed prevalence of 17.3% and 10.0% ($p<0.001$) respectively. Again, this was a young cohort with mean age of 39 years. Using a logistic model that included age, HIV-parameters, sociodemographic factors and markers of comorbidity they showed that frailty was associated with HIV-positive status, with higher risk at lower CD4 counts; and increasing age where participants over 50 had 3.71 times the risk of frailty compared to those under 30 (OR=3.71, 95% CI=1.74-7.92). Adverse social factors including smoking and low annual income as wells as comorbid conditions namely hypertension, renal and liver dysfunction were associated with frailty [191].

Akgun and colleagues utilised the VACS population to retrospectively assess frailty using an adapted FP akin to that used in MACS, comprising four of the five FP parameters (physical shrinking, exhaustion, slowness, and decreased physical activity), all of which were based on baseline survey data with no

objective measures recorded. In this cohort (n=3472 with HIV, 3043 without) with mean age 49.2 and majority male (>97%) participants they showed a low frailty prevalence of frailty of 2.9% of all HIV+ participants compared to 2.8% if HIV-. Amongst those with HIV, prevalence was higher in those with detectable virus (>400 copies) than if undetectable at 3.9% and 2.0% respectively [192]. The study did not focus further on predictors of frailty so we cannot compare risk factors to those discussed earlier in the chapter other than to say that in this cohort HIV status was not a clear predictor. The prevalence here is lower than that seen in the other studies, including MACS from which the phenotypic criteria were derived. The authors suggest as explanation that VACS represents a more contemporary cohort, with higher treatment experience than that seen in MACS particularly. However, it remains lower than that seen in other cross-sectional studies and may be related the proxy retrospective phenotypic characteristics used. Certainly the decreasing frailty prevalence reversed with the addition of grip strength measurement in MACS [176]. This approach to frailty measurement was felt to have internal validity however, as presence of frailty on the aFRP predicted both hospitalisation (HR=1.78, 95% CI: 1.48 to 2.13) and mortality (HR=1.75, 95% CI: 1.28-2.40) [192].

These additional sources further demonstrate the heterogeneity across those studies using FP variants and the failure to examine and report common associations. Association with HIV serostatus and prevalence of frailty are in keeping with that reported earlier, with only Akgun et al. reporting a lower prevalence that was not associated with HIV-status in VACS [192]. Similar associations in terms of depression, comorbidities and markers of social disadvantage have once again been demonstrated. However, new insights are provided in terms of the association with frailty and low BMI, high WHR and food insecurity, which may support the pathophysiological role of nutrition and adverse body composition changes that were suggested by Fried et al. in their conceptualisation of frailty [9].

2.4.2 Alternative ways of defining frailty in HIV studies

The FP or modified versions are not the only frailty assessment tools that have been utilised in studies including PLWH. Talukdar performed a retrospective

review of 567 newly diagnosed older adults with HIV in Kolkata, India. They defined frailty based solely on unexpected weight loss, which is probably insufficient to capture the multi-dimensional nature of frailty [193]. Ruiz et al. examined frailty in 20 PLWH aged over 60, selected to enter an urban 'geriatrics-HIV' clinic in New Orleans, US. Frailty was divided into mild, moderate and severe based on the presence of deficit in one, two or three or more domains respectively from personal ADLS (pADL), instrumental ADLs (iADL), mobility, nutrition, depression, cognition, hearing and vision. No participants were 'non-frail' with 30% having severe frailty [194]. A cross-sectional study from an academic clinic in New York, US, recruited 40 patients aged ≥50, stable on ART, mobile without walking aids, with no recent AIDS defining events or unstable/severe comorbidities. They defined frailty as the presence of ≥2 of the following criteria; Physical Performance Test score 18-32, peak oxygen uptake of 11-18ml/kg per minute or assistance with ≥2 iADLs or one pADLs. On this basis 60% (25/40) were frail, which was associated with higher levels of metabolic diseases (hypertension, hyperlipidaemia and diabetes) and higher BMI, waist circumference and trunk fat supporting a relationship with lipodystrophy [195].

Guaraldi's group have designed and applied a frailty index made up of 37 non-HIV variables and applied it to 720 participants (mean age 46.8; 32% women). They demonstrated that it predicted survival and incident multimorbidity independent of HIV or behavioural factors [120]. The VACS cohort includes all HIV+ US military male veterans receiving care in the Veterans Health Administration system, enrolled between 1997 and 2009. Data from this cohort has been used to develop the VACS index (VACSI), a biomarker based index comprising HIV factors (CD4, VL), hepatitis C status and routine laboratory parameters of haemoglobin, platelet count, renal and liver function. This approach aims to capture multisystem dysfunction and has been used as a marker of frailty. It has been shown to predict adverse outcomes that are observed in frail individuals, namely, hospitalisation [192], all-cause mortality [196] and fragility fracture [197].

Table 2.3: Description of additional HIV studies exploring frailty prevalence and predictors in HIV-positive individuals

Study	Study design	Frailty assessment	Prevalence	Frailty predictors
Akgun, 2014. USA [192]	Veterans Aging Cohort Study. HIV+/HIV- N=6515, mean age 50	Retrospective FRP with 4 criteria: shrinkage, low activity, exhaustion, slowness. Frail if ≥3/4 criteria.	2.9% HIV+ (2.0% HIV-)	Not examined. Frailty associated with mortality and unplanned admission.
Gustafson, 2015, USA [191]	Cross-sectional, HIV+/HIV- women in WIHS. N=2028, mean age 39	Prospective modified FP. Self-report: weight loss, exhaustion, low activity. Measured grip and walk speed. Frail if ≥3/5 criteria.	17.3% HIV= (10.0% HIV-)	Demographic: older age, smoking, low income HIV: HIV-serostatus. current CD4 <500 Comorbidity: hypertension, renal/liver dysfunction
Kooij, 2015[190] Netherlands	AGEhIV Cohort study. HIV+/HIV- aged >45. N=1144, median age 52	Prospective modified FP as used by Onen et al. Frail if ≥3/5 criteria[180].	10.6% HIV+ (2.7% HIV-)	Demographic: female sex Body composition: BMI<20, higher waist:hip ratio Comorbidity: depression, chronic Hepatitis C
Smit, 2015. USA [189]	Cross-sectional, HIV+ >45 years enrolled to CARE study. N=50, mean age 57	Prospective modified FP as used by Onen et al. Frail if ≥3/5 criteria[180].	16% HIV+	Demographic: older age, female sex Food insecurity Low physical activity
Guaraldi, 2015. Italy[120]	Retrospective cohort study. Modena metabolic HIV clinic. N=2722, mean age 46	Frailty index comprising 37 variables.	Mean FI 0.31 Frailty cut-off undefined	FI increased with: age, nadir CD4, VACS index
Ruiz, 2011 USA [194]	Cross-sectional. HIV+ attending geriatrics-HIV programme. N=20, median age 63.5	Frail if ≥1 deficit from cognition, ADLs, nutrition, depression, mobility, sensory impairment. Frailty graded mild (1) to severe (≥3 deficits)	100% frail 20% mild 50% mod 30% severe	Not assessed
Shah, 2012. USA [195]	Cross-sectional, HIV- outpatients >50 stable ART. N=40, mean age 58	Frail if ≥2 of: 1) Physical performance test score 18-32. 2)VO_2 max 11-18ml/kg/min. 3) ADL impairment	60%	Body composition: higher BMI, waist circumference and trunk fat
Talukdar, 2013. India [193]	Cross-sectional, new HIV, aged >50. N=567	Unexpected weight loss	31%	Not assessed

2.4.3 Conclusion:

The FP continues to be the most utilised tool in assessing frailty in HIV research settings. The addition of non-phenotype based studies would contribute to considerable heterogeneity that exists despite a ‘common diagnostic tool’. Therefore, the FP was chosen for the study described in this thesis with comparator variables drawn from the presented literature. There may however be a role for alternative frailty measures in terms of clinical practice and in predicting adverse outcomes, where in particular, the index based tools may have a role.

Chapter 3 - Methods

3.1 Study design

We designed and undertook a multi-centre, prospective cohort study conducted over a 24-month period from October 1st 2014-October 1st 2016. Baseline screening and recruitment was undertaken from October 1st 2014, with recruitment closing on the 30th September 2015. This thesis presents cross-sectional data collected at the time of the baseline visit.

3.2 Study setting

Participants were identified and recruited through five HIV clinics located in three NHS trusts across Sussex. They were, Western Sussex Hospitals NHS Foundation Trust; Central Clinic, Worthing and The Fletcher Unit, St Richard's Hospital, Chichester. Brighton and Sussex University Hospitals NHS Trust; the Lawson Unit, Brighton and East Sussex Healthcare NHS Trust; Station Plaza Clinic, Hastings and Avenue House Clinic, Eastbourne. We planned to recruit 300 participants.

3.3 Ethical considerations

The study was approved by South Central, Hampshire B Research Ethics Committee, reference 14/SC/0051. The study was sponsored by Brighton and Sussex University Hospitals NHS Trust and received Research and Development approval from all three NHS trusts involved. The study was conducted in adherence to Good Clinical Practice in research. A participant information sheet was supplied to each potential participant and signed informed consent was received from all participants at the baseline study visit (visit one), prior to completion of any study related activities. Details of ethical approval and participant information can be found in Appendix 2.

3.4 Eligibility criteria

Inclusion criteria:

- Documented HIV infection (either taking or naïve to cART)
- Age ≥50 years
- Ability to understand study patient information literature and comply with the requirements of the study

Exclusion criteria:

- Age <50
- Inability to understand or comply with requirements of the study- including cognitive impairment to a degree that capacity is impaired (investigator opinion). This is in line with other frailty studies, as cognitive impairment may cause a false impression of frailty in the absence of multi-system pathology.
- Current or inter-current illness or non-elective hospital admission reducing usual physical functioning in the last six weeks. This attempted to ensure all frailty assessments were based on true functional ability, rather than transient deterioration secondary to acute insult. Participants could have delayed entry to the study after recovery.
- Current chemo- or radiotherapy for active cancer. Again, this could cause a false representation of frailty secondary to these therapies, rather than multi-system age-related dysfunction that is the hallmark of frailty.
- Active participation in an intervention trial for a novel drug compound.

3.5 Study population and recruitment

Our aim was to recruit a study population reflective of the current UK demographic for HIV-positive individuals aged ≥50. Data on demographic mix was provided by direct communication from an enquiry to the Health Protection Agency in 2012. Of PLWH accessing care in the UK aged ≥50, 78% were male and 22% female. Of men in this age group, 77% identify their ethnicity as white and 63% acquired HIV through sex with other men and 31% through heterosexual intercourse. In comparison, 59% of women are of black African ethnicity, with 26% white. Amongst women, 94% of cases were acquired through heterosexual intercourse. Therefore, we aimed to recruit at least 66 women. A multi-centre study approach was chosen in an attempt to recruit a demographic mix representative of the UK HIV-cohort.

A list of eligible individuals was generated at each study site by the clinicians in charge, minimising unnecessary transfer of patient identifiable data. The

researcher was not involved in the identification of potential participants. Eligible patients were invited to participate on a consecutive basis at the time of clinic appointment. Recruitment ran for a one-year period (October 2014-October 2015), during which time all patients would have attended routine clinic follow-up at least once, providing all patients the opportunity to be informed of the study in an attempt to minimise sampling bias.

3.6 Study visits

3.6.1 Baseline visit (visit one)

Participants were contacted by the researcher and those expressing interest in progressing to study entry were screened for eligibility, and if inclusion criteria were met they were invited for the baseline (visit one) appointment at their local HIV clinic. Here eligibility was once again confirmed, the participant information sheet reviewed and consent received. Study activities were conducted per protocol including completion of the study questionnaire, a food frequency questionnaire, a paper based neurocognitive battery, a computer-based simple reaction time test, completion of the case report form (CRF) for medical and HIV history, and several measurements of body composition and frailty status.

3.6.2 12-month follow-up visit (visit two)

All participants attended for a second in-person visit at or as close to 12 months from their baseline visit as was practicable. Here the study questionnaire was repeated and CRF updated for changes in social and health status including new diagnoses, non-elective hospitalisations, and drug changes. The neuropsychological battery and frailty assessment were repeated and adverse events associated with frailty were captured, including:

- Falls since last contact (amount, nature, any injuries, particularly fracture)
- Non-elective admission to hospital (location, reason, duration)
- Level of function
- Admission to institutional care (nursing or residential, including respite)
- Death (date and cause to be confirmed by deaths certificate)

Follow-up visits were ongoing during the preparation of this thesis and as such data from visit two will not be presented.

3.6.3 DEXA-visit

A sub-group of participants were invited to attend an additional visit for a Dual-energy X-ray absorptiometry (DEXA) scan to formally assesse body composition. This was evaluated with whole body DEXA, using a GE full-body iDEXA with Lunar iDXA software version 11.40.004. Estimations of both whole body and regional (trunk and appendicular/limbs) lean mass and fat mass were calculated.

We aimed to conduct DEXA scans on all of those classified as frail as well as twice the number of age and gender matched subjects in the non-frail groups. The same scanner, based in the Clinical Investigation and Research Unit (CIRU) of the Royal Sussex County Hospital (RSCH), was used for all participants. Radiographers were blinded to frailty status of the participant.

3.7 Frailty assessment

Our primary outcome of interest in this cross-sectional study was the presence or absence of frailty. This was used to calculate the frailty prevalence for this cohort. Frailty was assessed using a modified frailty phenotype, adapted from the original proposed by Fried [9] and employed by Onen *et al.* in their investigation of frailty in HIV [180], which has been subsequently utilised in the HIV frailty research [10]. Table 3.1 shows the five frailty criteria and their scoring. The main adaptation from the original phenotype is to replace the assessment of low physical activity with a simple self-report question rather than the Minnesota Leisure Time Activity Questionnaire employed by Fried.

Table 3.1: Modified frailty phenotype criteria

Criterion	Definition			
Exhaustion [a]	Q: How often have you felt that:			
	Everything was an effort or I could not 'get going'			
	A: Occasionally (3-4 days) or most of the time (5-7 days)			
Low physical activity [b]	Q: 'Does your health limit vigorous exercise?'			
	A: Yes, limited a lot.			
Weight loss	Self-reported unintentional weight loss of >4.5kg in the last year			
Weak grip strength [c]	Male BMI	Grip (kg)	Female BMI	Grip (kg)
	≤ 24	≤ 29	≤ 23	≤ 17
	24.1-26.0	≤ 30	23.1-26.0	≤ 17.3
	26.1-28.0	≤ 30	26.1-29.0	≤ 18
	>28	≤32	>29.0	≤ 21
Slow walking time [c]	Male height (cm)	Seconds	Female height	Seconds
	≤ 173	≥ 7	≤ 159	≥ 7
	> 173	≥ 6	> 159	≥6

[a] Question originated from the Center for Epidemiologic Studies Depression Scale (CES-D) as used in Fried et al.[9]
[b] Question originated from the Short Form-36 quality of life questionnaire first used to define this criterion by Onen et al.[180]
[c] Cut-off values originated from Fried et al.[9]

Grip strength was measured using a Jamar hand held dynamometer. Grip strength was performed with the arm in neutral position with thumbs facing upwards. Patients were excluded if they suffer from debilitating musculoskeletal conditions of the hand or are experiencing pain [198]. Three recordings were performed with the maximum strength in kilograms recorded to one decimal place, the mean of three grips in the strongest hand was used to define weak or adequate grip as defined above based on gender and BMI.

Walking time was determined by the mean number of seconds taken to walk a marked distance of 4.57m twice. Timing started with the first footfall and stopped with the participant's first footfall after the end line [199]. Those unable to walk were excluded and the patient deemed 'frail' for this part of the assessment.

Each criterion was scored, with those scoring on none considered robust, those with one or two prefrail and the presence of three of more criteria denoted frailty. Patients were blinded to their frailty status throughout the study period.

3.8 Potential frailty predictors

We examined a number of parameters, which may be potential predictors or risk factors for frailty in PLWH. These were drawn from the existing literature of frailty in those with and without HIV. A broad selection of parameters was investigated across many biological, psychological and social domains to reflect the multidimensional nature of frailty and to mimic a comprehensive geriatric assessment, which one might receive in clinical practice.

A summary of the information collected at baseline is presented in the sections below, with more specific details provided from section 3.9.

3.8.1 History

Collected through use of a self-reported questionnaire and direct questioning were: personal demographics of date of birth, gender, ethnicity, sexual orientation, county of birth, education, as well as socio-economic (employment, housing and financial status) and lifestyle factors, inclusive of current/past cigarette smoking detailed in pack years (where one pack year is equivalent to smoking 20 cigarettes/day for one year), alcohol use with weekly estimated units and recreational drug use in the preceding 12 months or intravenous drug use ever.

A full clinical history was taken, including past and active medical comorbidities (including but not restricted to: cardiovascular, diabetes mellitus, neuropsychiatric, chronic viral hepatitis, liver disease, chronic kidney disease, airways disease, neuropathy and malignancy, both AIDS and non-AIDS defining) as well as a separate enquiry in to falls and fractures. A detailed HIV history was obtained, documenting duration and date of seroconversion if known, antiretroviral history (past, present and overall duration [taken from time commencing ART, including mono- or dual therapy]) and an ART adherence assessment, which asked the participant to rate their ART adherence on a scale from 0-100%, where 100% represents full adherence with no missed doses, and

where doses were missed, providing information on when a dose was last missed on an ordinal time scale.

A full drug history was taken to assess use of other non-antiretroviral drugs, including prescribed medications, over-the-counter drugs, herbal and/or nutritional supplements, other drugs acquired through other means.

Consent was received to permit access to medical records to confirm the information provided, particularly HIV parameters and ART regimen history, as well as allowing documentation of historical data such as peak (highest ever) viral load and virological suppression history, nadir (lowest ever) CD4 counts as well as documented opportunistic infections and AIDS defining events.

3.8.2 Examination

Physical examination included blood pressure measurement (estimated using automated sphygmomanometer, with the correct sized cuff), taken twice, with a five-minute interval and then repeated after standing for one minute. Corresponding heart rates were recorded. Anthropometrics measurements were taken including height (in metres); weight (in kilograms); waist and hip circumferences; mid-arm circumference; mid-thigh circumference; and skin-fold thickness at four sites (see section 3.12).

3.8.3 Study Questionnaires

Participants completed a composite study questionnaire that included the Short Form-12 (SF-12) assessment of quality of life [200], the Physical Activity Scale for the Elderly (PASE) [201], The Hospital Anxiety and Depression Score (HADS) [202], the short grit scale [203,204], the Lubben social network scale-6 (LSNS-6) [205,206], an 8-item purpose in life scale [207] and the prospective and retrospective memory questionnaire (PRMQ) [208]. Nutrition screening was assessed using the EPIC-Norfolk food frequency questionnaire (FFQ) (accessible at http://www.srl.cam.ac.uk/epic/nutmethod/FFQii.shtml) [209].

3.8.4 Neuropsychological battery

A neuropsychological battery included a computer-based simple reaction time alongside, the Montreal Cognitive Assessment (MoCA) [210], the National Adult

Reading Test (NART) [211], the trail making test [212] and a Controlled Oral Word Association Task (COWAT) [213].

3.8.5 Frailty and functional assessment

As mentioned the frailty assessment used was the frailty phenotype. Functional assessment included assessment of independence with personal and instrumental activities of daily living, as assessed by the Barthel [214] and Lawton [215] scales respectively.

3.8.6 Laboratory tests

Most recent laboratory tests, acceptable within 6 months of visit, were recorded. A change in blood testing protocols in individuals with HIV meant that only limited blood results were available for some individuals, however results considered core were:

- Full blood count (FBC)
- Liver function tests (LFTs)
- Creatinine
- Most recent CD4 and CD8 counts (cells/mm^3) and percentages, allowing calculation of the CD4/CD8 ratio within statistical software.
- Most recent HIV viral load (with undetectable taken as VL less than the lower limit of laboratory detectability, which was <40copies/ml for BSUHT and ESHT and <50copies/ml for WSHT patients).
- Serology for Hepatitis C (HCV)

Where available renal, bone, lipid, and thyroid profiles; glucose and HbA1c if known to be diabetic; vitamin D and parathyroid hormone levels and CRP were documented.

Optional consent was received to allow additional samples to be taken at baseline, including:

- Blood for CMV serology (presence or absence of CMV IgG reflecting infection, with documentation of arbitrary IgG units as a surrogate of anti-CMV activity)

- Blood for storage, to be used in the analysis of biomarkers, which have been associated with frailty and age-related NICM including IL-6 and C-reactive peptide (CRP).
- A buccal cheek swab to collect tissue for apolipoprotein-e4 (APO-e) gene analysis, which will be used in future analysis and not presented here.

3.9 Study questionnaires

3.9.1 Short Form-12 (SF-12) assessment of quality of life [200]

To assess health-related quality of life (HRQoL) we utilised version 2 of the Short-Form 12-Item Health Survey (SF-12) (licenced by QualityMetric Incorporated, Lincoln, RI), which is a validated and widely used measure of HRQoL providing insight into perceived physical and mental health status. The SF-12 is comprised of 12 items selected from the longer Short-Form Health Survey-36 [200]. It is a brief tool, which can be self-reported or administered by interview.

Table 3.2 shows the eight domains covered in the SF-12. Each question has either three or five responses, from which the participant is asked to select the answer that best describes how they perceive their current situation (defined as the last four weeks). Each question is scored separately as documented in the scoring manual and was undertaken using scoring software. Each domain is scored from 0 to 100, with 100 representing the highest HRQoL. Additionally, the domains can be summarised into the Physical Health Component Summary (PCS) and the Mental Health Component Summary (MCS) [216]. The PCS gives higher weights to general health, physical functioning, pain and role limitation due to physical health, whereas the MCS gives higher weights to measures of mental health including role limitation, energy and social functioning. The PCS and MCS are standardized to have a mean score of 50 and a standard deviation of 10 in a US reference population with higher values denoting better HRQoL.

Though the SF-12 is not specific for PLWH, it has been shown to be valid in this group [217]; has been used to assess HRQoL in key trials of ART strategies, namely START [218] and SMART [219] and is favoured for its brevity [220].

Table 3.2: The eight domains of the SF-12

Domain
1. General health
2. Physical functioning
3. Bodily pain (interfering with normal activity)
4. Role limitation, attributable to physical health
5. Role limitation, attributable to emotional problems
6. Mental health
7. Vitality/energy
8. Social functioning

3.9.2 Physical Activity Scale for the Elderly (PASE) [201]

The PASE is a tool designed to measure physical activity in individuals aged ≥65 years. It is a self-reported scale assessing exercise (number of days a week, and average hours per day), leisure, household and occupational activities over a 'normal' one-week period. It has been shown to be valid and reliable and has been utilised in individuals as young as 55 [221]. It has also been used as a surrogate measure of physical activity for the low activity criteria of the FP [138].

3.9.3 Hospital Anxiety and Depression Score (HADS) [202]

HADS is a validated tool that has been widely used to assess current symptoms of anxiety and depression. It is a self-reported scale comprised of 14 statements, seven pertaining to symptoms of generalised anxiety and seven to non-somatic depressive symptoms. Each statement is accompanied by four responses, which are scored on a scale of 0-3. Therefore, total scores range from 0-21 for anxiety and 0-21 for depression. Scores for symptoms can then be classified as normal (0-7), mild (8-10), moderate (11-14) and severe (15-21). Scores of 11 and above can be used to indicate a likely 'case' of mood disorder on each of the anxiety or depression scales [222]. HADS has been shown to be reliable and valid in assessing symptoms of depression and anxiety in community-based studies of PLWH [223], including in sub-Saharan settings [224]

3.9.4 Lubben social network scale-6 (LSNS-6) [205,206]

Limited social networks can lead to isolation and lack of social support. PLWH appear to be at risk of social isolation [225], which has been associated with adverse health-related outcomes in at least one large cohort [226]. The LSNS-6 is an abbreviated version of the original LSNS and comprises two identical sets of three questions, referring separately to family and then friendship ties. These questions, given here for family members, are: How many relatives do you see or hear from at least once a month? How many relatives do you feel close to such that you could call on them for help? How many relatives do you feel at ease with that you can talk about private matters? Participants are asked to respond with choices of none, one, two, three to four, five to eight or nine or more people for each question. These responses correspond to respective scores from 0-5, which are equally weighted and summed to generate an overall scale score from 0-30, where social isolation can be indicated by scores <12 overall or <6 on each of the two subscales, which on average indicates fewer than two individuals on each of the scale items. Internal reliability for the 6-item scale α=0.83, with reliability of the family questions α=0.84-0.89 and α=0.80-0.82 for the non-family questions [206].

3.9.5 Purpose in life scale [207,227]

Frailty reflects negative changes in many biological systems, which promotes a multidimensional approach when considering both its characterisation and consequences in individuals. Cognitive and psychological measures are often absent in this respect, however poor psychological well-being has been correlated with frailty [228]. Purpose in life has been considered a core component of psychological well-being [207], and can be used to describe that life has meaning and direction. We utilised a 10-item purpose in life scale derived from Ryff's scales of psychological well-being [207], operationalised in work by Barnes [229] and Boyle [227,230], demonstrating that greater purpose in life was associated with larger life space and reduced risk of cognitive impairment and mortality respectively. The scale's Cronbach coefficient α (0.73-0.75) indicates a moderate level of internal consistency. Table 3.3 shows the 10 statement questions, which were rated, in terms of agreement, on a scale of 1-5, which is reversed for negatively worded statements. The scores for each statement were totalled, with the mean

of the total taken as the score, with higher scores indicating greater purpose in life [230].

Table 3.3: The purpose in life scale

Statement
1. I feel good when I think of what I have done in the past and what I hope to do in the future.
2. I live life one day at a time and do not really think about the future.
3. I tend to focus on the present because the future nearly always brings me problems.
4. I have a sense of direction and purpose in life.
5. My daily activities often seem trivial and unimportant to me.
6. I used to set goals for myself, but that now seems like a waste of time.
7. I enjoy making plans for the future and working them to a reality.
8. I am an active person in carrying out the plans I set for myself.
9. Some people wander aimlessly through life, but I am not one of them.
10. I sometimes feel as if I have done all there is to do in life.

3.9.6 Short grit scale (Grit-S) [203,204]

Grit has been defined as 'perseverance and passion for long-term goals' [203]. It is possible that grit may influence psychological responses to ageing processes, contribute to well-being or predict those that are ageing more successfully, in this setting, in the absence of frailty. We utilised the Grit-S, a valid and reliable 8-item scale, where participants were asked to rate eight statements on a 5-point scale. Table 3.4 shows the statements presented to the participant. Positively worded statements were scored from 'very much like me'=5 to 'not like me at all'=1, which was reverse scored for negative statements. Statement scores were totalled and divided by 8 to provide a mean ranging from a maximum score of 5 (extremely gritty) to a lowest score of 1 (not at all gritty) [204].

Table 3.4: The short grit scale

Statement
1. New ideas and projects sometimes distract me from previous ones.
2. Setbacks don't discourage me.
3. I have been obsessed with a certain idea or project for a short time but later lost interest.
4. I am a hard worker.
5. I often set a goal but later choose to pursue a different one.
6. I have difficulty maintaining my focus on projects that take more than a few months to complete.
7. I finish whatever I begin.
8. I am diligent.

3.9.7 Prospective and retrospective memory questionnaire (PRMQ) [208]

Prospective memory relates to whether future plans are remembered at the appropriate time and retrospective memory to the content of completed or to-be-completed plans. Retrospective memory slips may be more widely reported, and although failures of either of these may have consequences, a detrimental example of prospective memory failure might be where one forgets to take a medication, which is vital in terms of ART adherence in PLWH. The PRMQ is a 16-item self-report tool measuring failures in pro- and retrospective memory in everyday life with the included statements shown in Table 3.5. Prospective and retrospective memory were represented by eight statements each, with each memory mistake rated on a five-point scale ranging from occurs very often (scores 5) to never occurs (scores 1). Scores were summed to give a total score ranging from minimum 16 to maximum 80, with separate scores generated for prospective and retrospective components. The scale has been shown to be reliable in terms of total, prospective and retrospective scores, which are not affected by age or gender [231]. Internal consistency using Cronbach's alpha is good at 0.89 (95%CI = 0.88-0.90) for the total scale, 0.84 (95%CI = 0.82-0.86) for the prospective, and 0.80 (95%CI =0.77-0.82) for the retrospective scales [231]. It has also been used in PLWH [232].

Table 3.5: Statements presented in the PRMQ separated by prospective and retrospective components

Statement
Prospective memory
Do you decide to do something in a few minutes' time and then forget to do it?
Do you fail to do something you were supposed to do a few minutes later even though it's there in front of you?
Do you forget appointments if you are not prompted by someone else of by a reminder such as a calendar or diary?
Do you forget to buy something you planned to buy, like a birthday card, even when you see it in the shop?
Do you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it's there in front of you?
Do you fail to mention or give something to a person that you were asked to pass on?
If you tried to contact a friend or relative who was out, would you forget to try again later?
Do you forget to tell someone something you had meant to mention a few minutes ago?
Retrospective memory
Do you fail to recognise a place you have visited before?
Do you forget something that you were told a few minutes before?
Do you fail to recognise a character in a radio or television show from scene to scene?
Do you fail to recall things that have happened to you in the last few days?
Do you repeat the same story to the same person on different occasions?
Do you mislay something that you have just put down like a magazine or glasses?
Do you look at something without realising you have seen it moments before?
Do you forget what you watched on television the previous day?

3.9.8 EPIC-Norfolk food frequency questionnaire (FFQ)

Nutritional deficits, particularly chronic undernutrition have been implicated in the pathophysiology of frailty [9]. There are many different methods of nutritional assessment, including the use of a FFQ, which have been utilised in a number of settings [233]. The advantage of the FFQ is that it can be self-completed and is less

burdensome for the participant than other tools, such as food diaries. FFQs have been utilised in HIV-positive populations [234].

There is no standard FFQ, the European Prospective Investigation of Cancer (EPIC), based in Norfolk, UK, designed a FFQ as a method of nutritional evaluation in this cohort, which has been validated elsewhere [235]. The FFQ is designed to measure a participant's usual food intake during the previous year. The FFQ is divided into two parts; the first lists 130 foods, with participants instructed to select how often they consume each food type from one of nine frequency categories ranging from “never or less than once a month” up to “greater than 6 times per day”. The second part includes types of specific foods including breakfast cereal, milk and fats. This FFQ was chosen due to its UK design and validation and ease of data analysis using open access FETA nutritional calculator [209].

3.10 Neuropsychological battery

3.10.1 National Adult Reading Test (NART) [211]

The National Adult Reading Test (NART) is an accepted and commonly utilised method of estimating premorbid intelligence. The test comprises 50 words with irregular pronunciation printed in order of increasing difficulty. Participants were asked to read aloud down the list with the number of pronunciation errors recorded. Scores were then used to predict intelligence quotient (IQ) using the formula: IQ= 127.7 – (0.826 x Number of errors) [211]. Average (Wechsler Adult Intelligence Scale) IQ ranges from 90-109.

3.10.2 Trail making test (TMT) [212]

The trail making test (TMT) can be used to measure a number of cognitive domains including processing speed, sequencing, mental flexibility and visual–motor skills. It is a timed paper and pencil task comprising two parts: In part A (Trails A) the participant was instructed to connect a sequence of 25 randomly distributed encircled numbers in ascending order (e.g. 1-2-3-4 and so on). In part B (Trails B) encircled letters were introduced alongside the numbers with participants instructed to alternately join the numbers and letters in sequential fashion (e.g. 1-A-2-B-3-C and so on). Participants were given the opportunity to practice each part to galvanise understanding. Both parts were timed, with

participants informed that they must correct any errors as they occur, thus incorporating adjustment for error within the task time. A recognised upper cut-off time of 300 seconds was applied, using this as the maximal time for completion [236].

3.10.3 Controlled Oral Word Association Task (COWAT) [213,237].

The controlled oral word association task (COWAT) is a common component of neuropsychological testing batteries, assessing verbal fluency. The purpose is to assess the spontaneous production of words within a given time limit. We utilised the F-A-S form of the test, where participants were given one minute to verbalise as many words as possible beginning with each of these three letters of the alphabet. Participants were instructed to avoid proper nouns (e.g. France, Frederick) or saying the same word with a different ending (e.g. fight, fights, fighting). The number of valid words for each of the three letters was summed to give the total score for analysis.

HIV-associated neurocognitive impairment has mainly been defined by negative performance in formal neuropsychological tests [238], which frequently incorporate both the TMT and COWAT [239,240].

3.10.4 Simple reaction time (SRT)

The SRT is a classic test of psychomotor speed measuring reaction time through the presentation of a known stimulus to the participant that should provoke a known response. In this study, we used a computer based test, which was set up to depict a plus sign centred horizontally and vertically on the computer screen to focus participants on the area where the stimulus was to be presented. They were asked to observe for the stimulus, which was depicted as the appearance of an ‘X’ in place of the plus sign, and respond by pressing the ‘space bar’ on the keyboard as quickly and as accurately possible. The stimulus occurred at varying time intervals, which were unpredictable to the participant. In this case, the task consisted of 48 trials, with a mask of varying length (300ms-1000ms) present between each target stimulus. All participants completed a practice task before moving on to the main scored task. RTs greater or less than 3 standard deviations (SD) from a participant’s mean RT were removed prior to analysis.

3.10.5 Montreal Cognitive Assessment (MoCA) [210]

The Montreal Cognitive Assessment was originally conceived as a tool for mild cognitive impairment (MCI). It is an open-access, one-page 30-point test, which can be administered in 10 minutes. It tests multiple cognitive domains: Short-term memory involved learning five nouns over two trials, with delayed recall after five minutes (5 points); Visuospatial ability was assessed using a clock-drawing task (3 points) and copying a three-dimensional cube (1 point); executive functions utilised an adapted Trails-B (1 point), a verbal fluency task (1 point), and verbal abstraction (2 points). Attention, concentration, and working memory were tested using a sustained attention task (finger tapping; 1 point), subtraction of serial-7s (3 points), and repeating digits forward and backward (1 point each); Language was assessed using naming of three animals (3 points), repetition of two complex sentences (2 points), as well as the fluency task; and lastly orientation to time and place (6 points). The score was adjusted for education of 12 years or less by addition of one point to the total, up to the maximum score of 30. A test score of 26 and above is normal, with 18-25 suggesting mild cognitive impairment and <18 indicating more severe cognitive dysfunction. The MoCA demonstrates good sensitivity (90%) and specificity (87%) for MCI, outperforming the Mini Mental State Examination (MMSE) [210].

The gold standard for diagnosis HIV-associated neurocognitive disorders (HAND) is formal neuropsychological testing and although the MoCA is not sufficient to diagnose HAND [241], it has potential as a screening tool [242,243].

3.11 Functional assessments

3.11.1 Activities of daily living (ADLs)

We examined both personal and instrumental activities of daily living (ADLs). Personal ADLs (pADLs) were assessed using the Barthel Index [214], which is a scale made up of ten items addressing personal care, feeding, mobility and continence. Each item was scored to reflect the participant's current actual level of function. The use of aids to maintain independence was allowed. The score for each item was summed to give an overall total, which has a range from 0-20. Lower scores indicate increased disability.

Instrumental ADLs (iADLs) were assessed using the Lawton scale [215]. This scale was used to rate participants' current functional ability regarding eight more complex activities integral for maintenance of independent living. A summary score ranges from 0 (low function, dependent) to 8 (high function, independent). Table 3.6 shows the items included in both the Barthel and Lawton scales. Scores below the maximal achievable for each respective scale indicates disability in either personal and/or instrumental ADLs.

Table 3.6: ADL domains included in the Barthel Index and Lawton Scale

Barthel pADLs	Lawton iADLs
1. Mobility	1. Using the telephone
2. Stairs	2. Shopping
3. Transfer	3. Preparing food
4. Feeding	4. Housekeeping
5. Bathing	5. Doing laundry
6. Grooming	6. Using transportation
7. Dressing	7. Handling medications
8. Toilet use	8. Handling finances
9. Bladder	
10. Bowels	

3.11.2 Additional functional tools

Markers of mobility and gait speed were assessed using patient history, falls assessment, and objective measures drawn from other frailty assessment tools including:

- Gait speed(m/sec) = 4.57/mean time for the timed walk in the FP
- Time to complete five times sit to stand test (5-SST), which was completed by asking the participant, seated on a standard chair, to raise from the chair to full standing and back down five times without using their arms. Participants were allowed a practice attempt, or a demonstration was provided and they were advised that they could forgo the test if they felt

unable to attempt or complete the task once started, which resulted in a failure in terms of scoring.

- Timed get up and go (TGUG), which begins with the participant seated and they were instructed on the sound of go, to stand and walk at a comfortable pace to a mark 3m from the chair, turn and return to be seated in the chair. The period from 'go' to return to a seated position was recorded in seconds.

3.12 Anthropometric measurements

Differences in body composition have been documented in PLWH compared to those without [244]. This has been particularly prevalent in those experiencing lipodystrophy, where individuals experience peripheral fat loss and/or central fat gain [245]. Adverse body composition parameters have been associated with adverse outcomes [246,247] and frailty [190]. We therefore elected to perform clinical measurements of body composition in all participants.

All measurements were performed in accordance with the National Health and Nutrition Examination Survey (NHANES) anthropometry protocol manual of January 2007 [248].

- Height was recorded in metres to 2 decimal places using a stadiometer or wall based measuring device with adjustable head piece.
- Weight was recorded in kilograms to one decimal place. Digital scales were utilised where possible. Where analogue scales were utilised, weight was recorded to the nearest 0.5 of a kilogram. Participants were weighed in light clothing with shoes removed if mobility and function allowed.
- Body mass index (BMI) was calculated within statistical software using the standard formula of weight(kg)/height(m)^2.
- Waist circumference was taken at level of upper part of iliac crests when felt for from behind. It was recorded in centimetres to one decimal place.
- Hip circumference was taken at level of biggest part of buttocks. It was recorded in centimetres to one decimal place.
- Waist to hip ratio was calculated in statistical software using the formula of waist circumference(cm)/hip circumference(cm).

- Circumferences were all measured in cm to one decimal place at three body sites:
    - Mid-thigh circumference, measured at the midpoint from inguinal crease to distal end femur.
    - Mid-calf circumference, measured at the maximal calf diameter.
    - Mid-arm circumference measured at the mid-point between the upper acromion to bottom olecranon with arm held by side, elbow flexed and palm up.
- Skin-fold measurements were taken using Holtain skinfold callipers and were measured to the nearest millimetre on a grasped fold of skin and adipose tissue at four body sites:
    - Triceps skinfold measured at the point of the mid-arm circumference on the posterior surface.
    - Subscapular skinfold measured 1cm below and medial to the inferior angle of the scapula with the participant standing and shoulders and arms relaxed at the side. The skinfold forms a line about 45 degrees below the horizontal extending diagonally toward the right elbow. The jaws of the calliper were placed perpendicular to the length of the fold for measurement.
    - Suprailiac skinfold measured at the iliac crest. The skinfold was taken so that it slopes downward and forward at a 45-degree angle extending toward the pubic symphysis. The calliper was again placed perpendicular to the skinfold for measurement.
    - Thigh skinfold measured at the point of mid-thigh circumference, taken on the anterior aspect of the thigh.

All measurements were taken where possible on the right-hand side and skinfold and circumference measurements were repeated twice for verification with mean recorded. Agreement was within 0.5cm.

Participants could opt out of the limb circumference and skinfold measurements if they considered them to be too intrusive. Some skin was too tight to form a skinfold comfortably and reliably. In both situations, these data were recorded as missing.

3.13 Statistical considerations

3.13.1 Sample size

At the time of study conception there was no reported frailty prevalence for a European HIV-positive population solely aged ≥50 therefore our sample size calculation is derived from precision based techniques, utilising prevalence data provided by the current literature base (prevalence ranged 8-20% as of 2012). We anticipated that frailty would be at the lower end of this range at around 10%. Therefore, to obtain a confidence interval of approximate width +/-3.5%, a sample size of 300 participants was chosen as our recruitment target. Table 3.7 shows the predicted confidence intervals for differing observed prevalence with a sample size of n= 300:

Table 3.7: Predicted confidence intervals based on precision-based sampling

Prevalence	Frail: Not frail	95% CI	Width of CI
8%	24:276	5.4; 11.6	+/- 3.10
10%	30:270	7.1; 11.9	+/- 3.41
12%	36:264	8.8; 16.2	+/- 3.69
15%	45:255	11.4; 19.5	+/- 4.04

3.13.2 Statistical analysis

Both continuous and categorical variables were summarized for all participants using descriptive statistics, presenting means with standard deviation for normally distributed variables, median with interquartile range for skewed continuous variables and proportions with percentages for categorical data. Based on Fried's phenotype, participants have been divided in to 'frail' (FP scores ≥3) or 'non-frail' (FP scores <3) for comparisons. Individuals were additionally divided into frail, pre-frail and robust patient groups (defined earlier), to allow the pre-frail group to be described and examined; this will provide ordinal data for comparisons. Individuals will be analysed based on their baseline frailty assessment, irrespective of any changes at reassessment. Age was utilised as both a continuous variable and divided into age strata of 50-59, 60-69 and >70 for analyses.

The analyses will utilise baseline data collected at the time of frailty status stratification, limiting impact of any losses. Comparison between categorical groups will be performed using Chi-square or Fishers exact tests (or Mann Whitney U test for ordinal data [frailty status]). Student's t-test will be used for normally distributed, continuous variables and Mann Whitney U test for non-normally distributed, continuous variables. Three group comparisons will use one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous and skewed data respectively. All p-values will be presented as 2-tailed and considered significant at $p < 0.05$. 95% confidence intervals will be provided for all parameters.

Based on initial univariate analyses, potential predictors of frailty status will be further evaluated using logistic regression analyses, applied to the comparator groups of frail versus non-frail and then frail, pre-frail and robust groups as defined above.

Data was collated in Microsoft Excel and all analyses for this thesis have been undertaken in Stata (Texas, USA) version 13 statistical software.

Chapter 4 - Prevalence and predictors of frailty

4.1 Introduction

It has been demonstrated that PLWH are experiencing frailty, with prevalence based on a phenotypic model of frailty ranging from 3.9-28% in the published literature to date [10,192]. Though not definitive due to methodological issues, using these studies we can start to build a picture of predictors of or associations with frailty in those with HIV. Table 4.1 summaries the predictors of frailty that have been demonstrated in individuals with HIV based on studies employing a frailty phenotype [10,11].

Table 4.1: Predictors of frailty in individuals with HIV

Frailty predictors	
Age	Smoking
Female gender	Falls
Black ethnicity	Functional impairment
HIV factors	Socioeconomic factors
Low current CD4 Low nadir CD4 Detectable viral load AIDS diagnosis	Lower educational attainment Unemployment Low annual income Food insecurity
Comorbidity	Body composition factors
Psychiatric disease Moderate-severe depression Chronic kidney disease Diabetes Liver dysfunction Hypertension Hepatitis C Cognitive impairment	Low BMI High BMI High waist to hip ratio Lipodystrophy

Chapter aims

The aims of this chapter are to:

- describe the study population and establish the cohort prevalence of frailty based on the described adapted frailty phenotype.
- examine factors associated with frailty across sociodemographic, medical, HIV, and functional domains utilising some of the key predictors identified from a systematic review of the literature.
- explore which factors may predict higher frailty states and thus more accurately identify frailty by comparing robust to prefrail and prefrail to frail groups.

4.2 Methods

4.2.1 Overview

Detailed description of the study design, including recruitment strategy has been provided in chapter three. To summarise we aimed to recruit 300 HIV-positive participants aged 50 years and over from five HIV clinics across Sussex, UK. Recruitment ran from 1st October 2014 to the 30th September 2015. All eligible participants provided informed consent and attended for a baseline visit where demographic details, medical and HIV backgrounds, psychosocial factor questionnaires and functional, including frailty, assessments were conducted.

4.2.2 Defining frailty

Frailty was assessed using a modified frailty phenotype [9,180], comprising five phenotypic criteria:

1. Low physical activity.
2. Exhaustion.
3. Unintentional weight loss.
4. Weak grip strength.
5. Slow walking speed.

The criteria were defined in section 3.7 and are repeated in Table 4.2.

Table 4.2: Adapted frailty phenotype criteria applied in this study

Criterion	Definition			
Exhaustion [a]	Q: How often have you felt that:			
	Everything was an effort or I could not 'get going'			
	A: Occasionally (3-4 days) or most of the time (5-7 days)			
Low physical activity [b]	Q: 'Does your health limit vigorous exercise?'			
	A: Yes, limited a lot.			
Weight loss	Self-reported unintentional weight loss of >4.5kg in the last year			
Weak grip strength [c]	Male BMI	Grip (kg)	Female BMI	Grip (kg)
	≤ 24	≤ 29	≤ 23	≤ 17
	24.1-26.0	≤ 30	23.1-26.0	≤ 17.3
	26.1-28.0	≤ 30	26.1-29.0	≤ 18
	>28	≤32	>29.0	≤ 21
Slow walking time [c]	Male height (cm)	Seconds	Female height	Seconds
	≤ 173	≥ 7	≤ 159	≥ 7
	> 173	≥ 6	> 159	≥6

[a] Question originated from the Center for Epidemiologic Studies Depression Scale (CES-D) as used in Fried et al.[9]
[b] Question originated from the Short Form-36 quality of life questionnaire first used to define this criterion by Onen et al.[180]
[c] Cut-off values originated from Fried et al.[9]

Participants can score from all to none of these parameters giving a potential score range of 0-5. These scores were then used to create three frailty categories as defined by Fried et al. where scoring zero classifies the person as robust; one or two as prefrail and three or more as frail [9]. In the main analyses for predictors we grouped those in the robust and prefrail categories (FP scores 0-2) together to form a 'non-frail' group. This allowed us to make comparisons between those with frailty and those without [180].

4.2.3 Defining predictor variables

Demographics

Several demographic details were collected including age, calculated as the time in years between the date of the baseline visit and the participant's date of birth.

Individuals were additionally divided into three age bands (<60, 60-69, and >70) to examine the frailty distribution across these groupings. Further demographic information was collected from the study questionnaire where participants were provided with a number of potential responses or an 'other option' for gender, ethnicity and sexual orientation. Ethnicity was divided into 16 options, within five broad categories of white, mixed ethnicity, black, Asian and other based on the NHS model of ethnicity data collection, which itself originated from the 2001 UK census [249]. Ethnicity was then grouped into white, black and other, and for multivariable analysis dichotomised to white or non-white.

Sexuality was divided into homosexual, heterosexual, bisexual, 'I don't usually use a term'/non-defined or any other term, which participants were asked to describe. It was important to capture the group representing men that have sex with men (MSMs), given that they make up the largest proportion of the UK HIV-positive demographic. MSMs were taken to be those self-identifying as homo- or bisexual and those males preferring not to use a label who on notes review their HIV acquisition was ascertained to be via sexual intercourse with other men.

Participants reported their country of origin and first language, which were dichotomised to be UK or Non-UK born and English first language or other first language respectively.

We asked all participants to report the number of years they had spent in formal education, taking 11 years to be the UK norm. They were then asked to identify their highest level of educational attainment from no formal qualifications through to university degree or above. An option of other was provided, which was mainly utilised for professional qualifications. Educational attainment was dichotomised to standard schooling or less (completed secondary school examinations or national equivalent if non-UK born; or left with less than 11 years of education or with no formal qualifications) compared with higher educational attainment (gained further or higher educational achievements).

Participants were asked to report their employment status divided into employed (full or part time) or not working, inclusive of those defining themselves as retired. Financial situation was assessed by enquiring as to whether the participant has

sufficient income to cover their basic needs (i.e. monthly food costs, rent, basic household bills) all, most, some or none of the time. Insufficient income was taken to be present if the individual could not cover the cost of these basic needs all the time. Housing situation was selected from home owner, rental accommodation, temporary housing, homeless or other and was dichotomised for analyses purposes as home ownership or not. We enquired as to household make-up dichotomising individuals to living alone or living with others.

Lifestyle risk factors included smoking status, defined as current, previous or never smoked. For those with a smoking history, pack years were calculated, with one pack year equivalent to smoking 20 cigarettes/day for one year. Intravenous drug use (IVDU) was classified as any prior exposure. Any recreational drug use in the prior year was recorded, including the drug types used. Lastly frequency of alcohol use and estimated number of units consumed weekly (if that frequently) was recorded. Standard definitions of alcoholic units were used.

HIV factors:

Clinical HIV notes were reviewed to ascertain accurate date of diagnosis, which was used to calculate duration of HIV in relation to date recruited to the study and age at diagnosis using their date of birth. Diagnosis age was dichotomised to above or below 50 years to examine the effect of diagnosis at older age. Nadir CD4 and most recent CD4 and CD8 cell counts were recorded, with the latter used to calculate the CD4/CD8 ratio. Nadir and current CD4 were used in continuous form and dichotomised as < or ≥350 cells/mm^3. The nadir CD4 count was taken as the lowest ever recorded, taken prior to the commencement of an adherent cART regime. Where available, CD4 cell count at time of diagnosis was recorded to ascertain late (<350 cells/mm^3) or very late (<200 cells/mm^3 or AIDS defining diagnosis) diagnosis. Peak and most recent viral load (copies/ml) values were taken, with undetectable viral load defined as a value below the highest of lowest detectable limit of the laboratories of the centres involved (taken as <50copies/ml). Any AIDS-defining events [250] and accompanying dates of diagnosis were recorded.

Date of commencement of any ART, along with current and all historical ART regimes, including any treatment breaks were recorded. Starting and current

regimens were particularly noted and classified as combination therapy, defined as at least three active antiretroviral drugs, usually two NRTIs and a third active antiretroviral agent (either an integrase inhibitor, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a boosted protease inhibitor (PI)) [45]. Date of commencement was used to calculate the duration of ART in years, taken from date initiated to date recruited. Delay to ART, in months, was calculated as the time from the date of diagnosis to the starting date of ART. Specific antiretrovirals were examined in more detail, due to their link with frailty in other studies or via their potential to cause body composition changes, or comorbidity, namely peripheral neuropathy. This included exposure to efavirenz, protease inhibitors (atazanavir, darunavir, ritonavir, saquinavir, lopinavir, indinavir, nelfinavir, fosamprenavir) and certain dideoxynucleoside type NRTIs, termed 'd-drugs', namely didanosine (ddI), stavudine (d4T) and zalcitabine (ddC)

Data was incomplete for some participants for the above parameters, particularly with respect to CD4 at time of diagnosis, nadir CD4, peak viral load and date of commencement of ART, especially for individuals diagnosed early in the HIV epidemic or where they had initiated treatment in centres outside of Sussex.

Comorbidities

Comorbidities have been defined and collected differently across the HIV and frailty studies. Appendix 3 shows a table of how comorbidities were classified in the studies included in the systematic review presented in chapter 2. We elected to use a combination of these, as well as additional comorbidities to be more inclusive as we were dealing with an older cohort.

Comorbidity data was broadly self-reported by participants, with some diagnoses corroborated by use of typical medication for specific comorbidities or gathered from notes and routine blood test review, such as chronic kidney disease. The self-report approach has been employed in a number of the studies investigating frailty in PLWH [94,175,176,179,181], which has been shown to be a valid means of gaining comorbidity information [251]. All comorbidities were documented as reported and a core number of common comorbidities contributed to overall comorbidity counts and included for analysis. Comorbidity counts have been

utilised as a means to evaluate and control for the confounding effect of comorbid disease[252,253]. Table 4.3 shows those comorbidities, with working definitions that determined comorbidity scoring. Liver disease other than active HCV was excluded due to inconsistencies in self-reporting. Multimorbidity was classified as the presence of two or more of the listed comorbidities.

As an alternative means of assessing the burden of comorbid disease we used the Charlson Comorbidity Index (CCI). This is a composite index originally based on 19 comorbid conditions, simplified to 17 [254,255]. Each condition is assigned a weighting score from 1-6. One point was allocated to myocardial infarction, congestive cardiac failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, ulcer disease, mild liver disease and uncomplicated diabetes. Two points for hemiplegia or paraplegia, severe renal disease, diabetes with end-organ damage, any tumour, leukaemia or lymphoma (within 5 years). Three points were given to moderate-severe liver disease and six points for metastatic solid tumour or AIDS. The points were summed to provide the overall CCI score, with zero indicating no comorbidity and higher scores reflecting larger comorbidity burden[254]. Points were not allocated to AIDS in this study as AIDS-defining event information was collected and analysed as a separate parameter, in line with the protocol employed by Lohse et al. [256].

Table 4.3: Case definitions of comorbidities included in the comorbidity count

Comorbidity	Definition
Ischaemic heart disease	Including myocardial infarction or angina or history of coronary intervention, accompanied by use of long-term antiplatelet and/or anti-anginal therapies
Other cardiac diagnoses	Including atrial fibrillation, valvular heart disease or congestive cardiac failure
Peripheral vascular disease	Including history of claudication, lower limb arterial intervention or amputation, supported by use of long-term antiplatelet/anticoagulant therapy.
Stroke/TIA	History of neurovascular event, supported by use of long-term antiplatelet/anticoagulant therapy.
Hypertension	Self-reported history, using at least one standard antihypertensive agent.
Hypercholesterolaemia	Self-reported history, using at least one standard lipid-lowering agent
Diabetes mellitus	Type 1 or type 2 variants, accompanied by use of oral hypoglycaemic agents and/or insulin
CKD	Defined as an estimated glomerular filtration rate (eGFR) of <60ml/min/1.73m^2 on two or more samples at least 90 days apart. Subdivided based on eGFR into: CKD3a 45-59, CKD3b 30-44, CKD4 15-29 and CKD5 <15/renal replacement therapy.
Chronic lung disease	Including COPD (on long-acting inhaled anticholinergic), asthma (on regular inhaled steroids), obstructive sleep apnoea (nocturnal continuous positive airway pressure) and recurrent pulmonary emboli (on long-term anticoagulant)
Peripheral neuropathy	Self-reported, supported by use of neuropathic agents.
Cancer	Including haematological malignancies and non-AIDS defining solid organ tumours, excluding non-malignant skin cancers, carcinoma in situ and Kaposi's sarcoma. Corroborated with histological/imaging reports if possible.
Arthritis	Formally diagnosed osteoarthritis or inflammatory arthritis (rheumatoid, psoriatic, systemic lupus on disease modifying agents). Recorded separately and combined in analysis due to low numbers of the inflammatory subtype.
Osteoporosis	Self-report supported by standard antiresorptive therapy and t-score <2.5 on bone density scan where available.

Table 4.3: Case definitions of comorbidities included in the comorbidity count

Comorbidity	Definition
Inflammatory bowel disease	Formally diagnosed ulcerative colitis or Crohn's disease on immune modulating agents.
Active Hepatitis C	Defined as the presence of hepatitis C viral RNA.
Depression	Clinically diagnosed depressive disorder on current anti-depressant therapy or engaged in psychological therapy
Neuropsychiatric	Including epilepsy on long-term anticonvulsant therapy, neurodegenerative conditions or bipolar affective disorder or psychotic illness, taking appropriate medical therapy.

Mood symptoms were based on the anxiety and depression subset scores from the Hospital Anxiety and Depression Scale (HADS). Mild symptoms in either anxiety or depression are classified by a score of 8-10, moderate 11-14 and severe 15-21. Mild mood symptoms were present if a participant scored 8-10 on either the anxiety and/or depression scales or moderate-severe mood symptoms if they scored >10 on either scale. We classified moderate to severe anxiety and depression symptoms separately and recorded those with a current history of diagnosed depression.

Cognitive status was examined using the Montreal Cognitive Assessment (MoCA), which has a score range from 0-30. Cognitive scores were used in continuous fashion and dichotomised to from a categorical variable based on a normal (≥26) or abnormal (<26) MoCA score.

Prescribed medications:

All participants were asked to bring along a list or their current prescribed medications to the baseline visit. All medications, doses and indications were transcribed and classified as being taken regularly (continuous with daily or alternative regular administration) or when required (such as analgesia, bronchodilators etc.). Inhaled, topical and parenteral medications were still considered regular if they were administered routinely. A total count of all regular medications was made. Compound medications, which contain more than one active drug, contributed the number of active drugs within the same preparation

to the total. For example, Atripla contains tenofovir, emtricitabine and efavirenz and would therefore contribute three drugs to any total. Totals were created for all medications, inclusive of antiretrovirals and for non-antiretroviral medications separately. The presence of polypharmacy was defined as the use of five or more regular medications.

Functional parameters

Participants were asked to report whether they perceived themselves to have a problem with their mobility or consider themselves to have care needs on a day-to-day basis. Disability was assessed based on impairments in personal ADLs using the Barthel Index and instrumental ADLs using the Lawton Score, dichotomised in both cases to absent (full marks achieved on the respective scales) or present (less than full marks). Participants were asked whether they had fallen in the last year, with a fall defined as an event whereby the individual unintentionally came to rest on the ground or lower level.

Pain was assessed and a participant was considered to be experiencing troublesome pain if they responded moderate, quite a bit or extremely to the question ‘During the past 4 weeks, how much did pain interfere with your normal work or activities?’ from the short form-12 survey.

4.2.4 Statistics

Questionnaire and case report form data were collected on pre-printed individually barcoded forms that were scanned and read using Formic Fusion software, with confirmatory entry of all numerical and text data. Data was stored and cleaned in Microsoft excel and imported to Stata version 13.0 for all statistical analyses. Calculations and formation of categorical variables were performed within these programmes.

Frailty prevalence was calculated based on the proportion of frail individuals in relation to the full cohort population size. Prevalence was also determined for prefrail and robust states. Prevalence values were accompanied by 95% confidence intervals to infer broader population prevalence range. Distribution prevalence of the five frailty criteria was described.

4.2.4.1 Descriptive statistics

The analysis strategy has been described in section 3.13.2. To summarise, the main analyses compared non-frail (robust and prefrail) and frail groups, with supplemental analyses using the three frailty categories. All categorical data were described using cross-tabulation with presentation of proportions with associations tested through use of Chi-squared tests with appropriate degrees of freedom.

After examining continuous variables for normality, those normally distributed variables were presented with mean and standard deviations, with 2-sided t-tests used for comparative statistics of two groups and one-way ANOVA for three group analyses, where appropriate assumptions were met. Where distributions were skewed, median and interquartile ranges were presented and non-parametric Mann-Whitney U test and Kruskal-Wallis test used for two and three group comparisons respectively.

All p-values will be presented as 2-tailed and considered significant at $p<0.05$. 95% confidence intervals will be provided for all parameters.

4.2.4.2 Univariate analysis

Univariate logistic regression was undertaken to establish crude odds ratios (OR) for frailty for each of the proposed predictor variables, with associated 95% confidence intervals.

4.2.4.3 Multivariable analysis

Predictor variables were grouped and assessed for multicollinearity within Stata version 13.0, utilising the variance inflation factor (VIF), with values greater than 4 indicating multicollinearity [257]. If present, the variables contributing to the highest VIF were examined and those deemed to provide the least clinically relevant insight into frailty were dropped from further analyses until VIF values for the remaining variables were below 4.

The multivariable logistic regression model, has been designed on the basis of permitting one parameter into the model for every 10 outcome events observed in order to maintain statistical power [258]. The primary outcome in this study is the

presence of frailty. Based on 48 outcome events, four parameters can be entered into the multivariable model without losing statistical power.

To select these parameters potential confounders were considered from the original list of variables. Though not consistent across the HIV literature both age and gender have been widely shown to be associated with frailty [122,181,184]. Therefore, age as a continuous variable and gender, dichotomised to male or female (with males as the reference group) were the first two candidate variables for the model.

To identify additional key confounding variables, we considered the presence of a current CD4 count below 350, which has been one of the most consistently reported predictors of frailty in PLWH [10,172]. We also considered the presence of comorbidities and a marker of abnormal mood status, which we represented with the continuous comorbidity count and HADS scores respectively.

Simple logistic regression and Mantel-Haenszel methods were used to assess the potential confounding effect of these selected parameters on the other predictor variables for frailty. Likelihood ratio tests (LRT) were then utilised to assess the contribution of each variable to the strength of the multivariable model, with a significant LRT ($p<0.05$) suggesting that inclusion of the parameter strengthens the model. This was the case for comorbidity count, HADS score and age but not gender or CD4 count below 350. Gender was included as the forth parameter in the multivariable model as it showed higher levels of confounding effect in stratified analysis, compared to CD4 count below 350.

This multivariable logistic model was used to produce odd ratios (OR) for frailty adjusted for age, gender, number of comorbidities and HADS score for each of the predictor variables. OR will be presented with their 95% confidence interval, with statistical significance considered where $p<0.05$. It should be noted that there was insufficient power to evaluate interaction in this model.

4.3 Results

4.3.1 Study population

Recruitment took place from the 1st October 2014 to the 30th September 2015. 253 participants of the target 300 were recruited representing recruitment of

84.3%. Participants were drawn from all the five the contributing HIV centres, with the majority, 176/253 (69.6%) recruited from the Lawson Unit, Brighton. Recruitment at the remaining centres in Eastbourne, Hastings, Chichester and Worthing was 28/253 (11.1%), 18 (7.1%), 16 (6.3%) and 15 (5.9%) respectively.

Table 4.4 shows the basic demographic details for the full cohort. The median age of the cohort was 59.6, with range from 50.1 to 87.3 years. Most participants were male at 90.9%. Of males, 95.2% were of white ethnicity and 85.7% identified as homo- or bisexual, which have been grouped to together in the category of MSM. Recruitment of women was below target at 23 (9.1% of the cohort). Females were majority of black ethnicity (60.9%) and heterosexual in terms of sexual identity (91.3%).

In terms of HIV parameters, the mean age of diagnosis was 46, with a mean duration of diagnosed HIV infection of 14.9 years. Over a third were diagnosed over the age of 50. In general, this is a treatment experienced and well controlled HIV-positive cohort with 97.2% on ART, achieving viral suppression in 96.8% and a mean current CD4 count of 656. Seven participants were not on ART, six of whom are completely naïve to antiretrovirals and one with prior treatment experience.

Anonymised clinical data on 54 participants who gave permission to be contacted for the study but later either declined or could not be contacted were provided by clinical staff. The median age of this group was slightly younger at 55 years with similar age range, 50-85. The male to female percentages matched the study population at 90.7% males and 9.3% females, though there was a higher proportion of non-white ethnicity in those not participating at 14.8%. HIV parameters were similar with median current CD4 of 624, HIV duration of 14.5 years and median time on treatment of 11.4 years. There was a slightly higher proportion with AIDS diagnoses in the non-participating group at 37% compared to 30.8%.

Table 4.4: Study population demographic and HIV characteristics

Variable	N (%) [a]
Age [b]	59.6 (IQR 54.9-65.6)

Age Range		50.1-87.3
Age group:	50-59.9	131 (51.8)
	60-60.9	94 (37.2)
	>70	28 (11.0)
Gender:	Male	230 (90.9)
	Female	23 (9.1)
Ethnicity	White	231 (91.3)
	Black	14 (5.5)
	Other	8 (3.2)
Ethnicity males	White	219 (95.2)
	Black	3 (1.3)
	Other	8 (3.5)
Ethnicity females	White	9 (39.1)
	Black	14 (60.9)
Sexuality males	MSM	197 (85.7)
	Heterosexual	27 (11.7)
	Use another/no label	7 (2.6)
Sexuality females	Bisexual	1 (4.4)
	Heterosexual	21 (91.3)
	Use another/no label	1 (4.4)
Age of diagnosis (years) [c]		46.0 (sd 10.47; range 25.0-80.2)
Diagnosed aged ≥50		91 (36.0)
HIV duration (years) [c]		14.9 (sd 8.07; range 0.33-32)
Current CD4cell count [c]		656 (280)
CD4cell count	≥350	225 (88.9)
	<350	28 (11.1)
Antiretroviral therapy		246 (97.2)
Undetectable viral load		246 (97.2)
Undetectable viral load on ART		238 (96.8)
[a] unless stated	[b] median (IQR)	[c] mean (sd)

4.3.2 Frailty prevalence

Based on the modified frailty phenotype 48/253 participants were classified as frail, giving a frailty prevalence of 19.0% (95% CI 14.6-24.3). Pre-frailty was

present in 111 participants (43.9%; 95% CI 37.8-50.1) and 94 (37.1%; 95% CI 31.4-43.3) scored on no phenotypic criteria, making them robust.

The reported frailty classification corresponds to scores, based on the five phenotypic criteria as discussed, giving participants a score ranging from 0-5. Figure 4.1 shows the frequency distribution of these scores, demonstrating that the most common score was zero, obtained by 94/253 (37.2%), with decreasing frequency as the score increased. Only one participant (0.4%) scored on all five phenotypic criteria.

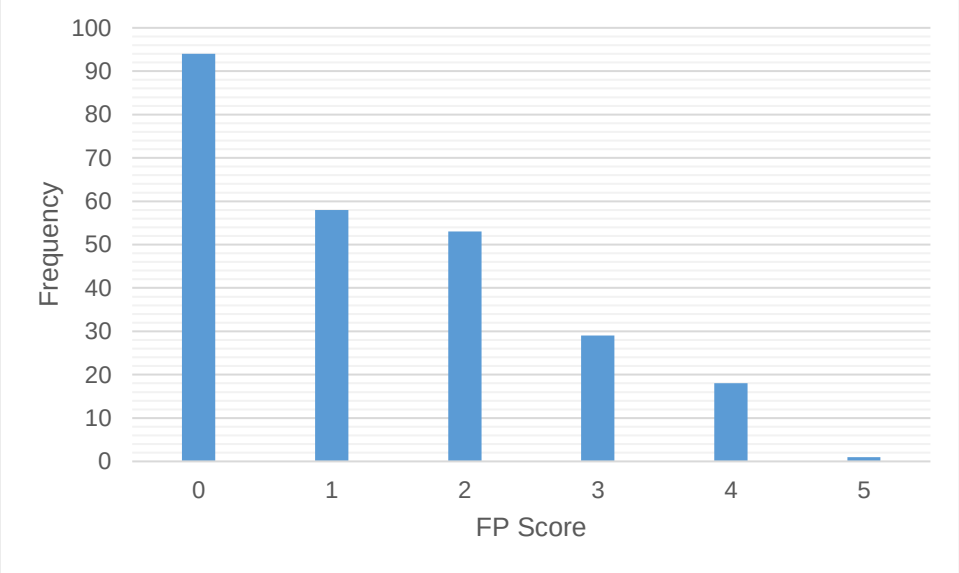


Figure 4.1: Frequency distribution of frailty phenotype scores

There was also variance in how commonly each of the individual phenotypic characteristics were reported. Figure 4.2 shows the overall prevalence of each of the frailty criteria across the full cohort, where low physical activity was the most prevalent, being reported by almost half of participants (47.1%), followed by exhaustion with 39.1%. The other criteria in decreasing prevalence were weak grip strength (22.5%), slow walking speed (10.7%) and unintentional weight loss (9.5%).

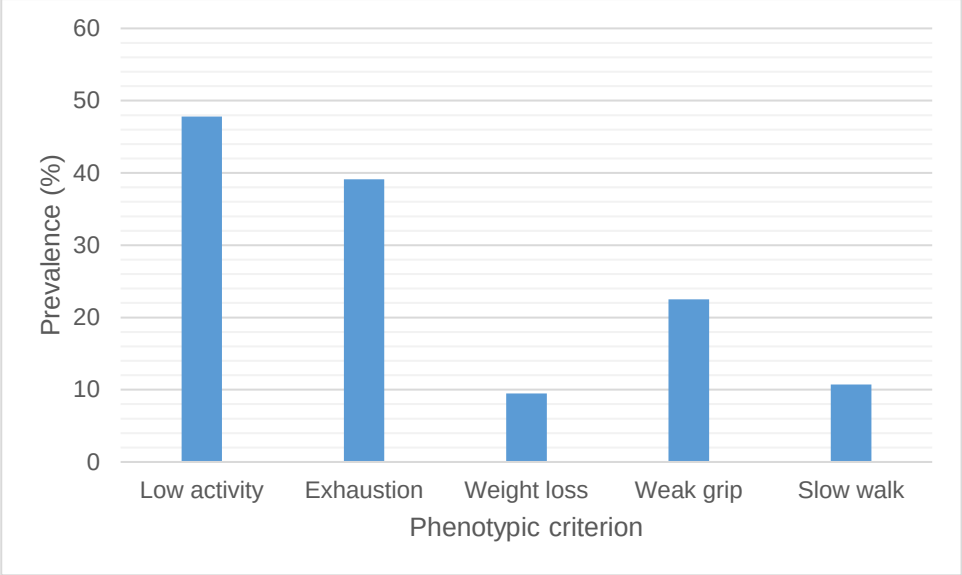


Figure 4.2: Prevalence of each frailty phenotypic criterion

Table 4.5 shows the prevalence of each criteria divided by FP score. The self-reported criteria of low physical activity and exhaustion are the most common reasons for scoring overall but particularly in those deemed prefrail (scoring one or two). The more objective measures of weak grip and slow walking speed become more prevalent in those with frailty (scoring ≥3).

Table 4.5: Distribution of frailty criteria by phenotypic score

		Frailty phenotypic criteria				
FP score	**N (%)**	**Low activity**	**Exhaustion**	**Weight loss**	**Weak grip**	**Slow walk**
0	94 (37.2)	-	-	-	-	-
1	58 (22.9)	27 (46.6)	18 (31.0)	5 (8.6)	8 (13.8)	0 (0)
2	53 (20.9)	48 (90.5)	39 (73.6)	4 (7.5)	10 (18.9)	5 (9.4)
3	29 (11.5)	27 (93.1)	26 (89.7)	5 (17.2)	22 (75.9)	7 (24.1)
4	18 (7.1)	18 (100)	15 (83.3)	9 (50.0)	16 (88.9)	14 (77.8)
5	1 (0.4)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
Overall	253 (100)	121 (47.8)	99 (39.1)	24 (9.5)	57 (22.5)	27 (10.7)

4.3.3 Cohort demographics by frailty status

Table 4.6 shows demographic characteristics and behavioural risk factors for the full cohort and for those with and without frailty. Those deemed non-frail are made up of the prefrail and robust groups (n=205). There was no statistically significant

difference in median age or in the age distribution seen when grouped into three age categories between the frail and non-frail groups.

Across the full cohort, participants spent a median of 12 years in formal education (IQR 11-16). Non-frail individuals reported a significantly higher median number of years in education compared to those with frailty, at 13 and 11 years respectively (p=0.019). Though not statistically significant, the non-frail group showed a higher proportion of those who continued education beyond standard schooling at 60% compared to 47% (p=0.127).

Almost two thirds (63.2%) of the cohort are either retired or were out of paid work at the time of surveying. Frail individuals were significantly less likely to be working with only 6.3% reporting being in paid work compared to 43.9% of those deemed non-frail (p<0.001 across work categories). Those with frailty demonstrated significant financial disadvantage, with 64.6% reporting a monthly income shortfall with respect to basic needs compared to 30.7% if non-frail (p<0.001). Though there was no difference in living alone, there was a significant difference in home ownership with non-frail individuals more likely to be home owners than their frail counterparts (68.8% versus 33.3%; p<0.001).

When examining behavioural risk factors, smoking was more common (p=0.05) and weekly alcohol use significantly less common (p<0.001) if frail, with no differences seen in recreational drug use in the previous year or lifetime experience of IVDU.

4.3.4 HIV factors by frailty group.

As described, this is a treatment experienced cohort with well-controlled HIV. Table 4.7 shows HIV demographic factors and certain antiretroviral information for the full cohort and then divided by frail and non-frail groups. Those with frailty had a statistically significantly lower mean nadir CD4 cell count at 117, compared to 180 if non-frail (p=0.027). Though not statistically significant, frail individuals have been diagnosed with HIV for longer (16.6 versus 14.5 years; p=0.094), had a higher prevalence of AIDS diagnosis (39.6% versus 28.8%; p=0.145) and were less likely to have been diagnosed at late stage of HIV (p=0.23) or have current CD4 counts over 350 (81.3% versus 90.7%; p=0.059) despite similar mean CD4

cell counts between the two groups. There were no differences in age at diagnosis or proportions diagnosed at older ages (i.e. over 50), CD4/8 ratio or viral suppression.

There were similar rates of antiretroviral therapy use between the groups, and although not statistically significant, the median duration of ART was longer for frail than non-frail participants at 14.6 and 11.4 years respectively (p=0.08). Those with frailty were significantly more likely to have been exposed to ‘d-drug’ NRTIs (didanosine, zalcitibine and stavudine) (p=0.025) and less likely to have efavirenz as part of a current ART regimen (p=0.06). There was no difference in current or historical exposure to protease inhibitors.

4.3.5 Non-infections comorbidities

Table 4.8 shows the frequency of NICM within the cohort and between frailty groups along with non-antiretroviral co-medication use. The presence of comorbidity was common with less than 20% of the full cohort having no comorbid conditions in addition to their HIV. Frail individuals had a statistically significantly higher number of comorbidities; were significantly less likely to have no comorbidities and more likely to have multimorbidity compared to those without frailty (p<0.001). The burden of comorbid diseases was also evaluated using the CCI, with frail participants showing statistically significantly higher scores in both the full and unadjusted forms (including and excluding age and AIDS diagnosis respectively).

With regards specific comorbidities, the most commonly reported were hyperlipidaemia (47.8%), peripheral neuropathy (27.3%), osteoarthritis (24.1%), and hypertension (24.1%). Prevalence of hyperlipidaemia, neuropathy, and osteoarthritis was statistically significantly higher for those who were frail, which was also seen for ischaemic heart disease, COPD, cerebrovascular event (stroke or TIA) and inflammatory arthritis, though numbers here were small.

Frail individuals take significantly more non-antiretroviral medications than those without frailty, taking a median of 5 and 2 drugs respectively (p<0.001). Additionally, 52.1% take five or more medications, defining polypharmacy, compared to 24.9% if non-frail (p<0.001).

Table 4.6: Demographic and behavioural characteristics by full cohort and frailty status

Variable		Full cohort N=253 (%)	Non-frail N=205 (%)	Frail N=48 (%)	*p*-value [a]
Age (years) [b]		59.7 (54.9-65.6)	59.6 (54-8-65.7)	60.3 (56.3-64.7)	0.483
Age group	50-59	131 (51.8)	109 (53.2)	22 (45.8)	0.657
	60-69	94 (37.1)	74 (36.1)	20 (41.7)	
	70+	28 (11.1)	22 (10.7)	6 (12.5)	
Gender	Male	230 (90.9)	189 (92.2)	41 (85.4)	0.141
	Female	23 (9.1)	16 (7.8)	7 (14.5)	
Ethnicity	White	231 (91.3)	190 (92.7)	41 (85.4)	0.240
	Black	14 (5.5)	10 (4.9)	4 (8.3)	
	Other	8 (3.2)	5 (2.4)	3 (6.3)	
Education (years) [b]		12 (11-16)	13 (11-16)	11 (11-14)	**0.019**
Standard education		107 (42.3)	82 (40.0)	25 (52.1)	0.127
Further education		146 (57.7)	123 (60.0)	23 (47.9)	
Living with others		143 (56.5)	120 (58.5)	23 (47.9)	0.182
Living alone		110 (43.5)	85 (41.5)	25 (52.1)	
Working		93 (36.8)	90 (43.9)	3 (6.3)	**<0.001**
Not working		67 (26.4)	43 (21.0)	24 (50.0)	
Retired		93 (36.8)	72 (35.1)	21 (43.7)	
Home owner		157 (62.1)	141 (68.8)	16 (33.3)	**<0.001**
No home ownership		96 (37.9)	64 (31.2)	32 (66.7)	
Income	Sufficient	159 (62.9)	142 (69.3)	17 (35.4)	**<0.001**
	Shortfall	94 (37.2)	63 (30.7)	31 (64.6)	
Non-smoker		200 (79.1)	167 (84.5)	33 (68.7)	0.051
Current smoker		53 (20.9)	38 (18.5)	15 (31.3)	
Recreational drug use		44 (17.4)	33 (16.1)	11 (22.9)	0.262
No drug use		209 (82.6)	172 (83.9)	37 (77.1)	
IVDU ever		13 (5.1)	12 (5.9)	1 (2.1)	0.287
No IVDU		240 (94.9)	193 (94.2)	47 (97.9)	
Weekly alcohol use		125 (49.4)	112 (54.6)	13 (27.1)	**0.001**
Less alcohol		128 (50.6)	93 (45.4)	35 (72.9)	

[a] p-value based on X^2 test unless stated.
[b] median (IQR); p-value based on MWU

Table 4.7: Relationship of HIV factors by frailty status

Variable		Full cohort N=253 (%)	Non-frail N=205 (%)	Frail N=48 (%)	*p*-value [a]
HIV duration (years) [b]		14.9 (8.07)	14.5 (7.96)	16.6 (8.38)	0.094
	0-9	77 (30.4)	66 (32.2)	11 (22.9)	0.194
	10-19	107 (42.3)	89 (43.4)	18 (37.5)	
	20-29	62 (24.5)	465 (22.0)	17 (35.4)	
	30+	7 (2.8)	5 (2.4)	2 (4.2)	
Age at diagnosis (years) [b]		46.0 (10.48)	46.2 (9.85)	45.2 (12.92)	0.574
Diagnosed aged ≥50		91 (36.0)	76 (37.1)	15 (31.3)	0.449
Diagnosed aged <50		162 (64.0)	129 (62.9)	33 (68.6)	
Late diagnosis	Yes	98 (38.7)	83 (40.5)	15 (31.3)	0.237
	No	155 (61.3)	122 (59.5)	33 (68.7)	
Nadir CD4(cells/mm^3) [c]		166 (90-252)	180 (101-258)	117 (59-200)	**0.027**
Current mean CD4 [b]		656 (280)	662 (276)	629 (304)	0.470
Current CD4	≥350	225 (88.9)	186 (90.7)	39 (81.3)	0.059
	<350	28 (11.1)	19 (9.3)	9 (18.8)	
CD4/8 ratio [c]		0.65 (0.43-0.91)	0.66 (0.43-0.92)	0.64 (0.45-0.83)	0.777
Viral load	Undetectable	239 (94.5)	192 (93.7)	47 (97.9)	0.245
	Detectable	14 (5.5)	13 (6.3)	1 (2.1)	
No AIDS events		175 (69.2)	146 (71.2)	29 (60.4)	0.145
AIDS diagnosis		78 (30.8)	59 (28.8)	19 (39.6)	
Current ART	Yes	246 (97.2)	199 (97.1)	47 (97.9)	0.748
	No	7 (2.8)	6 (2.9)	1 (2.1)	
ART duration [c]		11.7 (7.2-17.1)	11.4 (7.1-18.9)	14.6 (8.6-18.8)	0.080
Delay to ARV start (months) [c]		12 (1-52)	11 (1-53)	12 (1-48)	0.967
Current combined ART [d]		215 (87.4)	171 (85.9)	44 (93.6)	0.153
Current monotherapy		31 (12.6)	28 (14.1)	3 (6.4)	
No efavirenz in regime [d]		194 (78.9)	150 (75.4)	44 (93.6)	**0.006**
Current efavirenz use		52 (21.1)	49 (24.6)	3 (6.4)	
No PI in regime [d]		135 (54.9)	114 (57.3)	21 (44.7)	0.118
Current PI use		111 (45.1)	85 (42.7)	26 (55.3)	
No PI exposure [e]		89 (36.2)	77 (38.5)	12 (25.5)	0.096
PI exposure		157 (63.8)	122 (61.5)	35 (74.5)	
No d-drug exposure [e]		162 (64.0)	133 (66.5)	23 (48.9)	**0.025**
d-drug exposed		91 (36.0)	67 (33.5)	24 (51.1)	

[a] p-value based on X^2 test unless stated.
[b] mean (sd); p-value two-sided t-test
[c] median (IQR); p-value MWU
[d] n=246 on current treatment
[e] n=247 with prior ART experience

Table 4.8: Distribution of comorbidity by frailty status

Variable		Full cohort N=253 (%)	Non-frail N=205 (%)	Frail N=48 (%)	*p*-value[a]
Comorbidity count [b]		2 (1-3)	2 (1-3)	3 (2-5)	**<0.001**
Comorbidity	None	45 (17.8)	44 (21.4)	1 (2.1)	**<0.001**
	One	49 (19.4)	45 (22.0)	4 (8.3)	
	Multimorbidity	159 (62.8)	116 (56.6)	43 (89.6)	
Charlson comorbidity index [b]		0 (0-1)	0 (0-1)	0 (0-2)	**0.042**
Num. non-ART medications [b]		3 (1-5)	2 (1-4)	5 (4-7)	**<0.001**
Polypharmacy	<5 drugs	177 (70.0)	154 (75.1)	23 (47.9)	**<0.001**
	≥5 drugs	76 (30.0)	51 (24.9)	25 (52.1)	
Hypercholesterolaemia		121 (47.8)	91 (44.4)	30 (62.5)	**0.024**
Peripheral neuropathy		69 (27.3)	44 (21.5)	25 (52.1)	**<0.001**
Osteoarthritis		61 (24.1)	39 (19.0)	22 (45.8)	**<0.001**
Hypertension		61 (24.1)	47 (22.9)	14 (29.2)	0.363
Chronic kidney disease		40 (15.8)	32 (15.6)	8 (16.7)	0.857
Non-AIDS cancer		30 (11.9)	24 (11.7)	6 (12.5)	0.878
Diabetes		27 (10.7)	21 (10.2)	6 (12.5)	0.649
Ischaemic heart disease		23 (9.1)	15 (7.3)	8 (16.7)	**0.043**
Osteoporosis		19 (7.5)	11 (5.4)	8 (16.7)	**0.007**
Asthma		14 (5.5)	11 (5.4)	3 (6.3)	0.809
COPD		13 (5.1)	5 (2.4)	8 (16.7)	**<0.001**
Lymphoma		12 (4.7)	10 (4.9)	2 (4.2)	0.835
Stroke/TIA		12 (4.7)	7 (3.4)	5 (10.4)	**0.040**
Active hepatitis C		10 (4.0)	7 (3.4)	3 (6.3)	0.364
Inflammatory arthritis		5 (2.0)	2 (1.0)	3 (6.2)	**0.018**

[a] p-value based on X^2 test unless stated.
[b] Median (IQR); p-value based on MWU

4.3.6 Mood and cognitive status

Frail individuals have significantly more mood problems however defined. Table 4.9 shows mood and cognitive parameters recorded at the baseline visit. 50% of

frail participants had a formal diagnosis of depression (p<0.001) and had a median HADS score twice that of non-frail individuals (18 versus 8; p<0.001). Three quarters of those with frailty had at least mild anxiety or depression symptoms based on the HADS, with 47.9% and 22.9% having scores consistent with moderate to severe anxiety and depression respectively (p<0.001 for all comparisons). The frail group had statistically significantly lower scores on the Montreal Cognitive Assessment, with 35.4% having a score indicative of cognitive decline beyond age-related expectation (<26) compared to 18.5% in the non-frail group (p<0.001).

Table 4.9: Mood and cognitive markers in relation to frailty status

Variable	Full cohort N=253 (%)	Non-frail N=205 (%)	Frail N=48 (%)	*p*-value [a]
HADS score [b]	10 (6-17)	9 (5-15)	18 (14-23)	**<0.001**
Mod-severe mood symptoms	60 (23.7)	36 (17.6)	24 (50.0)	**<0.001**
Mild mood symptoms	111 (43.9)	75 (36.6)	36 (75.0)	**<0.001**
Mod-severe anxiety score	57 (22.5)	34 (16.6)	23 (47.9)	**<0.001**
Mod-severe depression score	21 (8.3)	10 (4.9)	11 (22.9)	**<0.001**
Diagnosed depression	72 (28.5)	48 (23.4)	24 (50.0)	**<0.001**
MoCA score [b]	27 (26-29)	27 (26-29)	26.5 (24-28)	**0.016**
Low MoCA (<26)	55 (21.7)	38 (18.5)	17 (35.4)	**0.011**

[a] p-value based on X^2 test unless stated.
[b] Median (IQR); p-value based on MWU

4.3.7 Functional parameters

Table 4.10 shows parameters pertaining to physical functioning. Frail individuals had statistically significantly higher reported daily pain and marked functional impairments. Almost 90% of those with frailty reported a mobility problem (89.6% versus 17.1%; p<0.001) and 75% had fallen in the previous year compared to 28.3% of those without frailty. There were low levels of non-mobility related functional disability overall, however frail participants were significantly more

likely to identify as having care needs for everyday tasks (56.3% versus 3.4%; p<0.001) and to have disability in personal (pADL) and/or instrumental activities of daily living (iADL) (p<0.001).

Table 4.10: Functional parameters by frailty status

Variable	Full cohort N=253 (%)	Non-frail N=205 (%)	Frail N=48 (%)	*p*-value [a]
Daily pain	98 (38.7)	62 (30.2)	36 (75.0)	**<0.001**
Mobility impairment	78 (30.8)	35 (17.1)	43 (89.6)	**<0.001**
pADL disability	30 (11.9)	11 (5.4)	19 (39.6)	**<0.001**
iADL disability	24 (9.5)	4 (2.0)	20 (41.7)	**<0.001**
Self-reported care needs	34 (13.4)	7 (3.4)	27 (56.3)	**<0.001**
History of falls	94 (37.2)	58 (28.3)	36 (75.0)	**<0.001**

[a] p-value based on X^2 test

4.3.8 Univariate analysis

All parameters were assessed for association with frailty status using univariate analysis. Age, gender and ethnicity did not predict frailty, however being out of work was associated with an almost 12-fold increase in the odds of frailty with crude OR 11.7 (95% CI 3.53-39.0, p<0.001). Financial insecurity and not owning one's home were both significantly associated with a 4-fold increase in frailty, with OR 4.11 (95% CI 2.12-7.97, p<0.001) and OR 4.41 (95% 2.26-8.60. p<0.001) respectively. Education was a protective factor with a 13% reduction in odds of frailty seen for each additional year of schooling (OR 0.87; 95% CI 0.78-0.97, p=0.04). No behavioural risk factor was associated with increased frailty risk, however weekly alcohol use appears to be associated with a 67% reduced odds of frailty compared to less frequent drinkers (OR 0.33; 95% CI 0.15-0.62, p=0.001).

No HIV factor predicted frailty in univariate analysis. When examining certain antiretroviral exposures, lifetime experience of 'd-drug' NRTIs was associated with a doubled frailty risk with an unadjusted OR 2.06 (95% CI 1.09-3.89, p=0.026).

The presence of comorbidity associated positively with frailty, with each additional comorbidity associate with increased odds of frailty by 63% (OR 1.63; 95% CI 1.35-1.96, p<0.001). This association was also seen using the CCI, where a one-point increase was associated with a 31% increase in frailty risk (OR 1.31; 95% CI 1.02-1.67, p=0.032). Some specific comorbidities were associated with increased odds of frailty including, in order of decreasing association, COPD (OR 8.0; 95% CI 2.49-25.72, p<0.001); peripheral neuropathy (OR 3.98; 95% CI 2.06-7.67, p<0.001); any arthritis (OR 3.79; 95% CI 2.01-7.13, p<0.001); ischaemic heart disease (OR 2.53; 95% CI 1.01-6.38, p=0.048) and hyperlipidaemia (OR 2.09; 95% CI 1.09-3.98, p=0.026). The odds of frailty increased by 39% for every non-antiretroviral medication taken (OR 1.39; 95% CI 1.23-1.57, p<0.001) and the presence of polypharmacy with non-antiretroviral prescribed medications was associated with a greater than three-fold increased odds of frailty (OR 3.28; 95% CI 1.72-6.28, p<0.001).

Abnormal mood was associated with frailty in univariate analysis. A one-point increment on the HADS score was associated with a 15% increase in frailty risk (OR 1.15; 95% CI 1.10-1.21, p<0.001), with scores suggestive of moderate to severe anxiety associated with a 4.6 times increased odds (OR 4.63; 95% CI 2.36-9.09, p<0.001) and moderate-severe depression a 5.8 times increase (OR 5.80; 95% CI 2.30-14.63, p<0.001). A current history of medically diagnosed depression was also associated with OR 3.27 (95% CI 1.70-6.28, p<0.001). Cognition also appears to be associated with frailty, with higher scores on the MoCA being protective (OR 0.84; 95% CI 0.75-0.94, p=0.002) and an abnormal score (<26) being associated with an increased likelihood of frailty (OR 2.41; 95% CI 1.21-4.80, p=0.012).

Markers of poor physical functioning were all associated with significant increased odds of frailty, including impairment in mobility (OR 41.77; 95% CI 15.44-113, p<0.001); personal ADLs (OR 11.55; 95% CI 4.99-26.73, p<0.001) and instrumental ADLs (OR 35.89; 95% CI 11.43-112.68, p<0.001). Fallers were more likely to be frail (OR 7.60; 95% CI 3.70-15.63, p<0.001), as were those with chronic pain (OR 6.92; 95% CI 3.37-14.19, p<0.001). Table 4.11 summarises the

crude relationships with core model parameters (age, gender, comorbidity count and HADS score) and frailty.

Table 4.11: Univariate analysis of core predictors of frailty used in multivariable model development.

Variable	crude OR	95% CI	*p*-value
Age (per year)	1.02	0.98-1.07	0.298
Female gender	2.02	0.78-5.22	0.148
Comorbidity count	1.63	1.34-1.96	**<0.001**
HADS	1.15	1.10-1.21	**<0.001**

4.3.9 Multivariable associations with frailty

A multivariable model was created with four core parameters of age, gender, number of comorbidities and continuous HADS score. Each potential predictor variable was fed into the model to provide an adjusted OR based on the core controlling parameters. Table 4.12 shows multivariable analysis including the core parameters and sociodemographic predictors. After adjusting for the core parameters, the strongest association with frailty remains the presence of comorbid conditions, with a 58% increased risk for each comorbidity (aOR 1.58; 95% CI 1.28-1.95, p<0.001). HADS score continues to be associated with frailty, with a one-point increase in score associated with a 17% increase in odds of frailty (aOR 1.17; 95% CI 1.01-1.21, p=0.018). Post-adjustment, we see that age is significantly associated with frailty, with frailty risk increasing by 6% per year (aOR 1.06; 95% CI 1.01-1.21, p=0.018). There is some evidence that women are three times more likely to be frail compared to men but this failed to reach statistical significance (aOR 3.16; 95% CI 0.95-10.51, p=0.06).

Though education had been associated with a significant protective effect in univariate analysis, this did not retain significance after adjusting for confounders. Ethnicity was not associated with frailty. The associations with work status, lack of home ownership and financial insecurity are reduced but retain significance. Financial insecurity predicted frailty with those with insufficient monthly income to meet their basic needs being 3.5 times as likely to be frail than those with

sufficient income (aOR 3.46; 95% CI 1.54-7.77, p=0.003), with similar risk seen for non-home owners (aOR 3.67; 95% CI 1.64-8.24, p=0.002). Those not working had an 8-fold (aOR 8.43; 95% CI 1.94-36.6, p=0.004) increase in frailty compared to those without.

Regarding behavioural risk factors, there was weak evidence that being a current smoker was associated with an increased frailty risk of about 2.4 times that of non-smokers (aOR 2.35; 95% CI 1.00-5.50, p=0.049). A history of IVDU was significantly associated with odds of frailty, however there was only one person in the frail group with IVDU experience, which is reflected by a very wide confidence interval (aOR 31.28; 95% CI 2.13-458.49, p=0.012). Neither alcohol nor recreational drug use were associated with frailty.

Table 4.13 shows the multivariable adjustment of HIV and ART parameters. The inclusion of a protease inhibitor in the current cART regime was the only factor retaining significance, associated with a doubling of the odds of frailty (aOR 2.09; 95% CI 1.06-5.13, p=0.036). Conversely regimens including efavirenz, were associated with lower odds for frailty (aOR 0.26; 95% CI 0.07-1.01, p=0.05). There was a trend toward an association with frailty in those with CD4 counts below 350, however this was of borderline significance (aOR 2.75; 95% CI 0.96-7.87, p=0.06). No other HIV or ART parameter showed significant association with frailty.

Table 4.12: Multivariable analysis examining the association of core model parameters and demographic factors and frailty

Variable	Adjusted OR [a]	95% CI	*p*-value
Age (per year)	1.06	1.01-1.21	**0.018**
Female gender	3.16	0.95-10.51	0.060
Comorbidity count	1.58	1.28-1.95	**<0.001**
HADS	1.17	1.10-1.24	**<0.001**
Non-White ethnicity	2.33	0.61-8.91	0.218
Education (by year)	0.91	0.81-1.04	0.158
Living alone	0.90	0.42-1.96	0.799
Not working	8.43	1.94-36.62	**0.004**
Financial insecurity	3.46	1.54-7.77	**0.003**
No home ownership	3.67	1.64-8.24	**0.002**
Current smoker	2.35	1.00-5.50	**0.049**
Recreational drug use	1.56	0.59-4.13	0.367
IVDU experience	31.28	2.13-458.49	**0.012**
Weekly alcohol use	0.55	0.24-1.30	0.177

[a] Adjusted for age, gender, comorbidity count and HADS score

Table 4.13: Multivariable analysis examining the association of HIV factors with frailty

Variable	Adjusted OR [a]	95% CI	*p*-value
HIV duration (per year)	1.00	0.95-1.05	0.943
Current CD4	1.00	1.00-1.00	0.384
CD4 count <350	2.75	0.96-7.87	0.060
CD4 nadir	1.00	1.00-1.00	0.243
Detectable viral load	0.30	0.28-3.31	0.327
AIDS diagnosis	1.35	0.61-3.01	0.456
ART duration (per year)	1.00	0.93-1.06	0.900
Age at diagnosis (per year)	1.00	0.95-1.05	0.943
Diagnosis aged over 50	1.46	0.54-3.97	0.460
Late diagnosis	073	0.33-1.61	0.434
Current protease inhibitor	2.09	1.06-5.13	**0.036**
Protease inhibitor ever	1.28	0.57-2.92	0.542
Current efavirenz use	0.26	0.07-1.01	0.051
D-drug exposure	1.44	0.64-3.28	0.379

[a] Adjusted for age, gender, comorbidity count and HADS score

We examined the association with markers of comorbidity and individual comorbidities which are shown in Table 4.14. After adjustment for core parameters, the CCI score was no longer associated with frailty, neither was the presence of polypharmacy for non-ART medications. However, the presence of non-ART medications was associated with a 22% increased odds of frailty for each additional medication taken (aOR 1.22; 95% CI 1.04-1.44, p=0.015). Regarding specific NICMs, the presence of COPD or arthritis were significantly associated with frailty with a 4.5-fold (aOR 4.53; 95% CI 1.11-18.60, p=0.036) and 3.6-fold (aOR 3.59; 95% CI 1.90-8.88, p<0.001) increased likelihood respectively. There was weak evidence for lesser frailty in those with

hypertension (aOR 0.40; 95% CI 0.16-0.99, p=0.048). Stroke, peripheral neuropathy, IHD and hyperlipidaemia had shown association in univariate but not multivariable analysis. After controlling for age, gender, comorbidity count and HADS score the MoCA score and mood parameters, including a history of diagnosed depression were no longer significantly associated with frailty status. Symptoms or anxiety and depression alone were not evaluated further due to collinearity with the total HADS score on which they are based.

Table 4.14: Multivariable analysis examining the association of comorbid disease factors with frailty

Variable	Adjusted OR [a]	95% CI	*p*-value
Charlson comorbidity index	0.90	0.61-1.34	0.611
Non-ART therapies (per drug)	1.22	1.04-1.44	**0.015**
Non-ART polypharmacy	0.89	0.35-2.25	0.803
COPD	4.53	1.11-18.60	**0.036**
Arthritis	3.59	1.90-8.88	**<0.001**
Hypertension	0.40	0.16-0.99	**0.048**
Stroke/TIA	1.75	0.40-7.74	0.461
Neuropathy	1.67	0.72-3.88	0.233
IHD	1.23	0.37-4.07	0.731
Hyperlipidaemia	0.86	0.36-2.03	0.731
Diagnosed depression	1.20	0.51-2.78	0.675
MoCA score	0.94	0.82-1.08	0.370
Low MoCA score (<26)	1.20	0.50-2.92	0.681

[a] Adjusted for age, gender, comorbidity count and HADS score

Table 4.15 shows the multivariable analysis of functional parameters after controlling for the core variables. All measures of functional assessment retained significance, with a 3-fold higher odds of frailty in those reporting chronic pain that interferes with daily activity (aOR 3.01; 95% CI 1.30-7.01, p=0.01) and falls

history with over four times increase in likelihood (aOR 4.25; 95% CI 1.86-9.74, p=0.001). Self-reported care needs or mobility impairment and measured pADL and iADL disability were significantly associated with increased odds of frailty; however the confidence intervals around each adjusted OR are broad.

Table 4.15: Multivariable analysis examining the association of functional parameters with frailty status

Variable	Adjusted OR [a]	95% CI	*p*-value
Daily pain	3.01	1.30-7.01	**0.010**
Personal ADL disability	6.53	2.40-17.82	**<0.001**
Instrumental ADL disability	18.76	5.53-63.65	**<0.001**
Self-reported care needs	25.03	8.32-75.3	**<0.001**
Mobility impairment	42.43	12.53-143.61	**<0.001**
History of falls	4.25	1.86-9.74	**0.001**

[a] Adjusted for age, gender, comorbidity count and HADS score

4.3.10 Risk factor associations across three frailty groups

As described, by employing a FP model, individuals can be classified as robust, prefrail or frail. To examine whether there were any key risk factors that differed between those that are robust and prefrail or prefrail and frail we repeated the analysis using these three frailty groupings. Table 4.16 shows the distribution of the potential frailty predictors for robust, prefrail and frail groups for demographic and HIV factors. Once again overall age profile does not vary across the groups. Though not significant, the proportion of females increases with increasing frailty states with 4.3%, 10.8% and 14.5% females in robust, prefrail and frail groups respectively (p=0.193), with a similar pattern seen for those of non-white ethnicity (p=0.09). There were significant differences seen in some socio-economic markers with years of education lower in frail participants (p=0.024) and levels of financial insecurity higher across the frailty groups with one quarter of robust participants reporting a financial shortfall compared to 36% in prefrail and 64.6% in frail individuals (p<0.001). Weekly alcohol use declined across the groups and smoking increased, though the latter failed to reach significance.

The mean duration of diagnosed HIV infection was lower (13.4 years) in the robust group, compared to 15.4 if prefrail and was highest in frail individuals at 16.6 years (p=0.05). The robust group saw the lowest cART usage at 93.6% with the corresponding lowest proportion of virally suppression, as measured by undetectable viral load, at 89.4% compared to over 97% for both parameters in prefrail and frail individuals. AIDS-defining events were more prevalent as frailty increased, however this and other parameter trends failed to reach statistical significance. Exposure to d-drug NRTIs and protease inhibitors increased with increasing frailty status with a converse relationship seen for current efavirenz use.

Table 4.17 shows the how parameters for comorbidities and functional status differ across the three frailty groups. Significant differences were seen in the number of comorbidities, proportion of those with multimorbidity, number of non-antiretroviral medications and presence of polypharmacy, with all increasing across the three frailty states ($p<0.001$ for all). The same pattern was observed for those individual comorbidities listed in Table 4.17. The HADS score increased significantly across the groups, as did the prevalence of moderate-severe anxiety and depressive symptoms, as well as formally diagnosed depression ($p<0.001$ for all). MoCA cognitive scores were negatively associated with frailty and decreased as frailty increased (p=0.001), with proportion of those with an abnormally low score rising from 11.7% in the robust group to 24.3% and the further to 35.4% in the prefrail and frail groups respectively (p=0.004).

Reports of chronic pain, self-perceived care needs, measured disability, mobility impairment and falls prevalence all increased with increasing frailty state ($p<0.001$ for all relationships).

Table 4.16: Examining the association of demographic and HIV parameters across three frailty groups

Variable		Robust N=94 (%)	Pre-Frail N=111 (%)	Frail N=48 (%)	*p*-value [a]
Age [b]		59.0 (55.3-65.1)	59.7 (54-4-66.2)	60.3 (56.3-64.7)	0.740
Age group	50-59	52 (55.3)	57 (51.4)	22 (45.8)	
	60-69	37 (39.4)	37 (33.3)	20 (41.7)	
	70+	5 (5.3)	17 (15.3)	6 (12.5)	0.193
Female gender		4 (4.3)	12 (10.8)	7 (14.5)	0.090
Non-White ethnicity		5 (5.3)	10 (9.0)	7 (14.6)	0.177
Education (years) [b]		13 (11-17)	13 (11-16)	11 (11-14)	**0.024**
Financial insecurity		23 (24.5)	40 (36.0)	31 (64.6)	**<0.001**
Not working		40 (42.6)	75 (67.6)	45 (93.8)	**<0.001**
Non-home ownership		17 (18.1)	47 (42.3)	32 (66.7)	**<0.001**
Current smoker		16 (17.0)	22 (19.8)	15 (31.3)	0.133
Recreational drug use		16 (17.0)	17 (15.3)	11 (22.9)	0.506
IVDU experienced		7 (7.5)	5 (4.5)	1 (2.1)	0.361
Weekly alcohol use		61 (64.9)	51 (45.9)	13 (27.1)	**<0.001**
HIV duration (years) [c]		13.4 (8.51)	15.4 (7.38)	16.6 (8.38)	0.050
Age at diagnosis [c]		46.8 (10.3)	45.7 (9.50)	45.2 (12.92)	0.648
Nadir CD4 [b]		180 (101-265)	179 (102-255)	117 (59-200)	0.067
Current mean CD4 [c]		641.8 (247.0)	679.1 (297.6)	629.3 (304.1)	0.492
Current CD4<350		8 (8.5)	11 (9.9)	9 (18.8)	0.161
AIDS defining event		22 (23.4)	37 (33.3)	19 (39.6)	0.106
Undetectable VL		84 (89.4)	108 (97.3)	47 (97.9)	**0.024**
Current ART use		88 (93.6)	111 (100)	47 (97.9)	**0.020**
ART duration [b]		10.8 (6.1-16.5)	11.6 (7.8-17.2)	14.6 (8.6-18.8)	0.061
Current efavirenz use		24 (25.5)	25 (22.5)	3 (6.3)	**0.021**
Current PI use		36 (38.3)	49 (44.1)	26 (54.2)	0.196
PI use ever		47 (50.0)	76 (68.5)	35 (72.9)	**0.006**
'd-drug' use ever		27 (28.7)	40 (36.0)	24 (50.0)	**0.044**

[a] p-value based on X^2 test unless stated.

[b] median (IQR); p-value based on Kruskal-Wallis test.

[c] mean (sd); p-value based on one-way ANOVA

Table 4.17: Comorbidity and functional parameters across three frailty groups

Variable	Robust N=94 (%)	Pre-Frail N=111 (%)	Frail N=48 (%)	*p*-value [a]
Comorbidity count [b]	1 (0-2)	2 (1-4)	3 (2-5)	**<0.001**
Multimorbidity	38 (40.4)	78 (70.3)	43 (89.6)	**<0.001**
Charlson index [b]	0 (0-0)	0 (0-2)	0 (0-2)	**<0.001**
Num. non-ART drugs [b]	1.5 (0-3)	3 (1-6)	5 (4-7)	**<0.001**
Polypharmacy	10 (10.6)	41 (36.9)	25 (52.1)	**<0.001**
P. neuropathy	9 (9.6)	35 (31.5)	25 (52.1)	**<0.001**
Arthritis	9 (9.6)	32 (28.8)	23 (47.9)	**<0.001**
COPD	0 (0)	5 (4.5)	8 (16.7)	**<0.001**
All cancer	6 (6.4)	28 (25.2)	7 (14.6)	**0.001**
Stroke/TIA	0 (0)	7 (6.3)	5 (10.4)	**0.013**
Osteoporosis	3 (3.2)	8 (7.2)	8 (16.7)	**0.016**
IHD	6 (6.4)	9 (8.1)	8 (16.7)	**0.017**
Hyperlipidaemia	37 (39.4)	54 (48.7)	30 (62.5)	**0.032**
HADS score [b]	7 (4-10)	12 (8-18)	18 (14-21)	**<0.001**
Anxiety	9 (9.6)	25 (22.5)	23 (47.9)	**<0.001**
Depression	1 (1.1)	9 (8.1)	11 (22.9)	**<0.001**
Diagnosed depression	13 (13.8)	35 (31.5)	24 (50.0)	**<0.001**
MoCA score [b]	28 (26-29)	27 (26-28)	26.5 (24-28)	**0.001**
Low MoCA (<26)	11 (11.7)	27 (24.3)	17 (35.4)	**0.004**
Daily pain	8 (8.5)	54 (48.7)	36 (75.0)	**<0.001**
Mobility impairment	4 (4.3)	31 (27.9)	43 (89.6)	**<0.001**
pADL disability	2 (2.1)	9 (8.11)	19 (39.6)	**<0.001**
iADL disability	0 (0.0)	4 (3.6)	20 (41.7)	**<0.001**
Self-report care needs	1 (1.1)	6 (5.4)	27 (56.3)	**<0.001**
History of falls	12 (12.8)	46 (41.4)	36 (75.0)	**<0.001**

[a] p-value based on X^2 test unless stated.

[b] median (IQR); p-value based on Kruskal-Wallis test.

[c] mean (sd); p-value based on one-way ANOVA

4.3.11 Multivariable analysis between frailty states

We applied our previously described multivariable logistic regression model to examine whether there were any key factors associated with higher frailty states by comparing robust to prefrail individuals and then prefrail to frail individuals. The lesser frail state was used as the reference group in each comparison pairing. Table 4.18 shows the output of this multivariable analysis. After adjusting for confounders we observed that the only mutual demographic factor reaching significance for an association with higher frailty was being out of work. The addition of an individual comorbidity was associated with an 86% increase in odds of prefrailty when compared to robust (aOR 1.86; 95% CI 1.43-2.42, P<0.001) and a 39% increase when comparing frail to prefrail (aOR 1.39; 95% CI 1.12-1.73, P=0.003). The presence of arthritis (inflammatory or osteoarthritis) was associated in a 2.3-fold and 3.6-fold increase in the likelihood of prefrailty and frailty respectively. An increase in one point on the HADS was associated with a 12% increase in prefrailty (aOR 1.12; 95% CI 1.06-1.19, P<0.001) and 14% increase in frailty risk (aOR 1.14; 95% CI 1.08-1.21, P<0.001). Self-reported mobility impairment and history of falls were both positively associated with prefrailty and frailty, with falls associated with around a 3-fold increase in odds of prefrailty (aOR 2.91; 95% CI 1.30-6.51, P=0.009) and frailty (aOR 3.36; 95% CI 1.44-7.82, P=0.005).

Female gender was associated with an almost 6-fold increase in odds of prefrailty (aOR 5.83; 95% CI 1.50-22.69, P<0.001), but was not significantly associated with frailty (p=0.192). An increased CCI score was associated with prefrailty but not frailty, as was a history of any cancer and the presence of chronic pain.

Age was associated with frailty but not prefrailty, with a 6% increase in the odds of frailty per year (aOR 1.06; 95% CI 1.00-1.11, P=0.034). As shown in the main analysis, frailty was three times as likely in those with financial insecurity (aOR 3.07; 95% CI 1.35-7.01, P=0.008) but again this did not predict prefrailty. Other associations with frailty only (when compared to the prefrailty state) were the use of non-antiretroviral co-medications, with a 20% increased risk per additional drug (aOR 1.20; 95% CI 1.12-1.73, P=0.029), as well as a diagnosis of COPD and the presence of disability in instrumental or personal ADLs and a perceived need for

care. There was weak evidence for less frailty for those taking a cART regime containing efavirenz (aOR 0.26; 95% CI 0.07-0.99, P=0.049).

Table 4.18: Multivariable analysis of predictors of high frailty states

	Robust-Prefrail			Prefrail-Frail		
Variable	**aOR [a]**	**95%CI**	***p***	**aOR [a]**	**95% CI**	***p***
Age (per year)	1.02	0.97-1.07	0.428	1.06	1.00-1.11	**0.034**
Female gender	5.83	1.50-22.69	**<0.001**	2.19	0.67-7.12	0.192
Not working	2.04	1.01-4.10	**<0.001**	6.33	1.46-27.5	**0.014**
Financial insecurity	1.36	0.67-2.78	0.397	3.07	1.35-7.01	**0.008**
Non-home owner	2.67	1.26-5.67	**0.011**	2.98	1.31-6.77	**0.009**
Current smoker	1.27	1.56-2.87	0.565	2.23	0.93-5.35	0.074
HIV duration (per yr.)	1.00	0.96-1.05	0.844	1.00	0.95-1.05	0.999
CD4count <350	1.04	0.34-3.13	0.946	2.47	0.83-7.36	0.105
Current efavirenz use	1.17	0.54-2.55	0.689	0.26	0.07-0.99	**0.049**
Comorbidity count	1.86	1.43-2.42	**<0.001**	1.39	1.12-1.73	**0.003**
Charlson index	1.07	1.08-2.62	**0.021**	0.87	0.59-1.29	0.497
Non-ART therapies (per drug)	1.68	0.75-1.10	0.326	1.20	1.02-1.41	**0.029**
COPD	- [b]	-	-	5.58	1.53-20.32	**0.009**
Arthritis	2.29	1.20-7.12	**0.018**	3.62	1.63-8.05	**0.002**
All cancer	3.99	1.40-11.34	**0.009**	0.46	0.16-1.35	0.157
HADs score	1.12	1.06-1.19	**<0.001**	1.14	1.08-1.21	**<0.001**
Chronic pain	5.12	2.07-16.68	**<0.001**	2.36	0.99-5.61	0.052
pADL disability	2.16	0.39-11.95	0.379	5.71	2.08-15.66	**0.001**
iADL disability	- [b]	-	**-**	14.53	4.31-48.96	**<0.001**
Care needs	2.01	0.21-19.32	0.545	23.20	7.25-74.22	**<0.001**
Mobility impairment	7.08	2.17-23.11	**0.001**	32.0	9.28-110.4	**<0.001**
Falls history	2.91	1.30-6.51	**0.009**	3.36	1.44-7.82	**0.005**

[a] adjusted for age, gender, comorbidity count and HADS score
[b] no events in this group to allow comparison

4.4 Discussion

In this cohort of 253 well-treated HIV-positive older adults we saw a frailty prevalence of 19%. This prevalence is at the higher end of the range previously observed in PLWH and is greater than we anticipated given that we are dealing with a treatment experienced cohort, who have access to and make use of free healthcare via NHS services, which might confer a more positive state of health. Additionally, we failed to reach our recruitment target and as such the confidence intervals for frailty are broader, at 14.6-24.3%, than our expected sample size precision of +/-3%. However, despite this, the frailty prevalence based on this confidence interval still sits within the range seen across the published studies at 2.9-28% [10,192].

The prevalence of 19% is comparable to a number of published frailty studies in PLWH using the phenotype method [175,179,181,186,191], particularly the US-based study by Ianas et al., where frailty was present in 19% overall and 16.7% for those over 50 [179]. However, there are important differences in some of the other study populations that may limit direct comparison. This includes Pathai's examination of frailty in a younger, predominantly female South African cohort, where overall prevalence was 19.4% with a studied population that was less treatment experienced with many likely differing exposures given the resource poor-setting [181]. Others have focussed on those with HIV in the context of prior intravenous drug use, which was low in our study, finding a frailty prevalence of 14.6% [175]; and lastly in the solely female Women's Interagency HIV Study (WIHS) it was 17.3% [191]. It should be noted that the average population ages were younger than described in our cohort.

The most comparable study to ours is the Dutch AGEhIV study, which found a lower prevalence at 10.6%[190]. Our prevalence of frailty is higher than has been found in this and other studies, despite a similar if not equivalent method of frailty assessment. There may be several contributing reasons, which reflect the main predictors of frailty identified in this cohort. These centre on the older median age, greater non-infectious comorbidity burden and high prevalence of mood disorder. Additionally, methodological issues surrounding ascertainment of frailty, which we have alluded to, may have contributed and will be discussed.

4.4.1 Frailty criteria

The individual frailty criteria varied in prevalence, with low physical activity being seen in 47.1% of all participants. Exhaustion was reported by 39.1% and the other criteria less so with 22.5% for weakness, 10.7% for slowness and 9.5% for unintentional weight loss. The breakdown of the phenotypic criteria has not been widely reported across the literature. In the original Cardiovascular Health Study, low activity was the most commonly reported criteria at 22%, with 20% demonstrating weak grip and slow walk, though the lowest quintile values were used to define cut-offs. 17% met criteria for exhaustion and 6% for weight loss [9]. Where reported in those with HIV, low activity was seen in 12-39%; 19-38% for exhaustion; 9-24% for weakness; 2-16% for slowness and 10-24% for weight loss [178,181,189,190]. Our cohort demonstrates higher levels of low activity and exhaustion compared to other cohorts but less unintentional weight loss.

Though low activity and exhaustion were higher than seen across other studies it should be noted that symptom burden amongst PLWH has been shown to be high. The UK based cross-sectional Antiretroviral, Sexual Transmission Risk and Attitudes study (ASTRA), examined symptoms, anxiety, depression, well-being and function in 3258 adults diagnosed with HIV [259]. Across the cohort, the most commonly reported symptoms were a lack of energy in 64.9% and tiredness in 64.6%, and when symptoms were grouped, 77.4% reported symptoms related to sleep/energy and tiredness [259]. These symptoms were more marked in those under 60, with a shift towards a differing pattern of symptomology at older ages, mainly around physical symptoms such as joint problems and pain, which if mirrored in our studies might go some way to explaining why frailty remains prevalent in those under 60. Additionally, weight loss as a self-reported symptom was reported by 16.7%, which caused distress in 35.3% of these [259].

Fatigue could be seen as a surrogate for exhaustion and has been used in alternative frailty screening tools such as the FRAIL scale [106]. Fatigue is a common symptom experienced by PLWH as described above and in studies investigating it and its correlates. Sullivan et al. performed a retrospective case review of 13,768 PLWH showing that fatigue sufficient to prompt medical appointment or impede everyday functioning including ability to work was present

in 37%, which was associated with depression, anaemia and clinical AIDS but not CD4 or VL [260]. A UK based cross-sectional study with 143 adults with HIV found that 65% had significant fatigue based on the Chalder fatigue questionnaire, which was strongly associated with symptoms of psychological distress (found in 68%), higher functional impairment and higher CD4 counts [261]. Lastly work from North Carolina, US, showed that prevalent and incident fatigue in those with HIV was associated with psychosocial over physiological factors, namely low income, unemployment, depression and anxiety and stressful life events [262,263]. This supports our finding of high levels of self-reported exhaustion and as described above there is an interconnection between symptoms of fatigue and function, which may present as low physical activity.

Additionally, the high prevalence of low activity may be a product of the way it was measured in this adapted phenotype, where an individual scored on this criterion if they felt their health limited them in performing strenuous activities. In the original phenotype, low activity was based on the Minnesota Leisure Time Activities Questionnaire which provides a quantitative measure of physical activity by converting reported activity in to metabolic equivalent values of energy usage. Therefore, the approach used in this study, which has been used by a number of other studies, may be prone to overestimate prevalence of this criterion, which may have elevated the number of participants meeting prefrailty and frailty criteria. The fact that low activity is higher than the other HIV studies may in part be explained by the older age of the cohort and higher prevalence of comorbidity and symptoms of mood disorder, which may all impede strenuous activity thus potentially reflecting a valid observation in this demographic that warrants further evaluation particularly in comparison to more objective measures.

4.4.2 Age and frailty

The median age of this cohort at 59.6 years, represents the oldest group reported on to date to our knowledge, with the average age of other studies ranging from 39-57 years [10]. We report on a cohort of solely older adults with HIV, with a range extending to 87 years old. This deliberate focus on older adults prohibits conclusions about the full age-range and has examined the relative effect of age

on frailty in an already older cohort. Though we did not see a difference in frailty by age and age group in descriptive and univariate analysis, after adjusting for gender, number of comorbidities and HADS score in multivariable analysis, increasing age was associated with frailty in this cohort with each additional year associated with a 6% increase in the odds of frailty. This negative confounding suggests that in the absence of comorbidity and symptoms of mood disorder age is a risk factor for frailty, which is seen in the non-HIV population [9,122]. Though not consistent, age has been associated with frailty in PLWH [179,180], particularly in women with a 2.5 times increase seen in South African women with HIV [181] and in American women in the WIHS [191]. In men enrolled to MACS, a 10-year increase in aged was associated with 52% increase in being frail at any point during follow up [184]; with the most recent assessment of frailty within MACS showing an increased proportion of study visits where frailty was demonstrated with increasing age [176]. Lastly, in the AGEhIV study, they only showed increased odds of frailty (aOR 4.10; 95% CI 2.53-6.64) in those aged >65 when compared to 45-50 [190].

Age may therefore be an important frailty predictor in PLWH, particularly at older ages above 65, which might be deemed a traditional 'geriatric' population. We have described frailty occurring at younger ages and because we are unable to comment on when frailty may have arisen we cannot delineate between premature frailty that may be secondary to HIV or frailty of old age, if such a distinction even exists. The older age distribution of our cohort may go some way to explaining the higher prevalence, as we would expect frailty to become more common with age, however it is unlikely to be the only reason as the prevalence still exceeds that seen in longitudinal studies of frailty of presumed HIV-negative individuals >65 at 10-14% [122–124].

4.4.3 Non-infectious comorbidity and frailty

The presence of medical comorbidity was high with 82.2% of individuals describing at least one chronic disease alongside their HIV, which was significantly higher for those with frailty at 97.9%, with 89% having multimorbidity. This compares to the presence of comorbidity in 71-89% of HIV-positive participants in frailty studies [176,180,190]. This is much higher than seen in general

population studies, including the Cardiovascular Health Study, where 67.7% of frail individuals aged ≥65 had multimorbidity [9], and in a large Scottish study of adults of all ages where the overall prevalence of multimorbidity of 23.2%, increasing to 64.9% of those over 65 [85]. Additionally, a community based-study of Australian men aged over 70 saw multimorbidity in 75% [264]. Therefore, our findings are in keeping with studies which show a higher occurrence of comorbidity and multimorbidity in PLWH, particularly at older age, which has been comparatively greater than HIV-negative individuals [5,72,73,265].

The comorbidities that were significantly more prevalent in those with frailty included hypercholesterolaemia, peripheral neuropathy, arthritis, COPD, IHD and cerebrovascular disease. After adjustment for factors included in our multivariable model, only COPD and arthritis were associated with a higher chance of frailty. Overall however, comorbidity did predict frailty, with a 58% increase in likelihood for each additional comorbidity present from our selected list of NICMs. The level of comorbidity seen in frail individuals in this study is higher than has been previously reported and given the strong relationship with frailty it may go some way to explaining the observed higher overall frailty prevalence.

COPD was associated with a 4.5-fold increase in the adjusted odds of frailty, although absolute numbers of individuals with a diagnosis was low at 13, representing 5.1% of the study population, which may explain the broad confidence interval around this effect size (95% CI 1.11-18.6). However, we cannot say this represents full case ascertainment as COPD may have gone unreported, reported as an alternate respiratory diagnosis such as asthma or be undiagnosed in the face of high smoking prevalence, particularly amongst frail individuals. HIV appears to be significant risk factor for COPD and other respiratory conditions [266,267] and similar associations between COPD and frailty have been seen in those with and without HIV, with an increased the odds of frailty between 2.2-3.0-times, which is greatest in those with COPD and HIV [268,269]. Arthritis was associated with a 3.6-fold increase in the odds of frailty (95% CI 1.9-8.9). Here we describe a composite of diagnoses, as only five individuals reported an inflammatory type arthritis as opposed to diagnosed osteoarthritis.

Again, many people reported joint symptoms that they believed to be arthritis yet we only included those who had had this confirmed by a medical professional. Osteoarthritis has been associated with frailty in HIV-negative older adults, increasing the odds of frailty by up to 3-times [270–272]. It has been studied less in the context of HIV, though arthritis is a commonly reported comorbidity in studies [273,274], and one group has shown it to be associated with frailty [178]. Both of these comorbidities through the associated symptoms could easily impact on functional ability and frailty criteria, making optimisation of these and other comorbidities a potential target for intervention in prevention of new or progressive frailty.

As in our study, increasing numbers of comorbidities as well as higher numbers of concomitant medications for these problems have been shown to be higher in PLWH with frailty compared to those without [175,178–180]. However, the associated contribution to frailty risk cannot be easily compared due to differences in methodology. For example, in the ALIVE study, multimorbidity rather than single comorbidity predicted frailty, when assessed using a comorbidity count [175]. Erlandson et al. again used a comorbidity count, showing that the presence of four or more comorbidities was significantly associated with frail compared to non-frail states [178]. In the AGEhIV study an increasing number of comorbidities was associated with around a doubling of the risk of higher frailty states, however this effect was nullified after controlling for the body composition parameter of the waist-to-hip ratio [190]. The fact that different studies showed different relationships with frailty and individual comorbidities may reflect choice of included comorbidities, case ascertainment, population characteristics, and statistical modelling, where different and in some cases, more comprehensive parameter inclusion into multivariable analysis strategies have been utilised.

We were limited using self-report for comorbid conditions, with the potential for misclassification of comorbidity count. However this approach has been used in the setting of HIV and frailty [175,176,179,181] and in investigation of multimorbidity in population studies [275]. We mitigated against over inflation by corroborating reported diagnoses with recognised treatments that participants may have been taking, achieved by reviewing their actual prescriptions or drugs, minimising recall bias. However, we did include some diagnoses that are not included in the

Charlson comorbidity index (CCI) or comorbidity lists that have been used before, particularly hypercholesterolaemia and peripheral neuropathy. Their inclusion is justified though by the fact that they are clinically relevant to individuals with HIV through their association with certain antiretrovirals, as well as their potential to drive pathology such as vascular and liver disease in the case of high cholesterol and functional and mobility issues for neuropathy. Additionally, where these have been included, hypercholesterolaemia has been found to be the most prevalent comorbidity in other study groups [4,176,179], with peripheral neuropathy also reported frequently [4,179].

Corroborating our approach in the use of a comorbidity count is the similar relationship seen when we used the CCI, which uses a standardised list of comorbidities, with a higher median score seen in frail individuals and a crude OR of 1.31 for a one-point increase in CCI. The relationship was not present in multivariable analysis however. This is may be expected as we controlled for comorbidities, which contribute to the score, even though there was no observed collinearity.

Conversely, we may have underreported comorbidity through our exclusion of liver disease and questioning around and requirement for usage of standard treatment, meaning 'lifestyle-controlled' comorbidities such as diabetes, hypertension and hypercholesterolaemia may not have been reported or recorded. We could have minimised recall bias further by fully examining paper-based medical notes, however this was not possible and indeed may not reflect all comorbidities as this still relies on optimal exchange of information with primary care, where many chronic disease diagnoses are made.

Fried et al. suggest that frailty and comorbidity are distinct yet overlapping entities [276]. Comorbidities may be the manifestation of physiological decline either globally or in specific organ systems, or they may be drivers of frailty through negative metabolic states that may occur due to their presence such as chronic kidney disease or diabetes or through adverse effects related to their treatments. As such, it may be that total number of comorbidities is more important than the individual comorbidity as seen in our results, where higher comorbidity burden may reflect a greater degree of underlying homeostatic dysfunction. Certainly,

this way of thinking fits with the concept of the frailty index, where frailty increases as the number of so called deficits increase. Each comorbidity can be included as a deficit within a frailty index and it is the cumulative effect of these deficits rather than the nature of any single one that is important in defining frailty [110].

4.4.4 Gender and frailty

There was a suggestion that female gender may be associated with increased odds of frailty, however it failed to reach statistical significance in multivariable analysis (p=0.06). This may be due to the low numbers of women recruited at only 23, of which seven were frail. Certainly in the AGEhIV study of Dutch older adults with HIV, male gender was protective for prefrailty or frailty with a 46% reduction seen when compared to females [190]. In those with current or prior IDU, women demonstrated a higher risk for frailty, however analyses included those with and without HIV [175]. There was no gender difference seen in other mixed groups [179–181] and in the studies focussed solely on women, frailty prevalence was not higher than that seen in male only or mixed cohorts [174,191]. This is slightly at odds with findings in frailty research within the general population where women appear to be at a higher risk of frailty [9,123,126,277].

4.4.5 Sociodemographic factors and frailty

Markers of adverse socioeconomic status have been shown to correlate with frailty across the HIV literature. These include the protective effect of higher educational attainment [176,180], which was echoed in this study where lower educational achievement was significantly more common in those with frailty with additional years of education reducing the odds of frailty in univariate but not multivariable analysis (p=0.16).

Markers of social disadvantage do appear to correlate with frailty in this cohort with increased odds of frailty seen for those not in work, not owning their home and who report financial insecurity. Financial insecurity was associated with a 3.5-fold increase in frailty likelihood (p=0.003), with a similar risk seen for those who did not own their own home, which may be a surrogate marker of lower financial status. Where the role of income has been examined there have been mixed findings. In two American studies defining a low annual income as <$12000, Erlandson et al. showed that being in this lowest income bracket did

not predict frailty when compared to the highest [178]. However, findings from the WIHS showed a 65% increase in the odds of frailty for those with low income [191], which is supported by work by Onen et al. where frail individuals were more likely to have earned <$10000 in the preceding year [180]. This relationship with low income and frailty has also been demonstrated in those without HIV [278–280]. In addition, socioeconomic disadvantage across the life course, particularly with respect to financial hardship is associated with adverse health status in older adults, including frailty [281] and functional limitations [282]. The association seen in this study should be taken with caution as our method relied on self-report of not having sufficient funds to cover basic living expenses rather than information regarding actual household income or an accurate picture of use of financial/welfare support in the form of benefits opening the potential for misclassification and overestimation of this relationship.

In this study, only 36.8% were employed either full- or part-time. Not being in work was associated with an 8-fold increase in the likelihood of frailty (p=0.004). This is a lower rate of employment when compared to the ASTRA study where 57.4% of the cohort were employed, however this cohort included all adults over 18 so encompassed a wider period of working age [259]. A German-based study of PLWH showed unemployment to be more prevalent than within the general population, with unemployment being associated with higher burdens of symptomatic HIV/AIDS, psychiatric disease and frailty as assessed by difficulties in managing daily activities [283]. Frailty by this measure was associated with a 4.7- and 3.2-fold increase in the odds of baseline unemployment and loss of job during the study period respectively ($p<0.05$) [283].

Importantly, in the data we present, not-working includes those that have retired, which was a heterogeneous group made up of those who have reached retirement age and those that took early retirement for any reason, which may include those who were ‘medically retired’. This same approach has been used elsewhere however [178] where it was shown to predict frailty. Whether unemployment contributes to or results from frailty is unclear, and the cross-sectional nature of this study prevents comment upon causation. We cannot exclude reverse causation, where frailty may impede one’s ability to work rather

than unemployment driving frailty, as seen in the study by Groß et al. where those in work and functionally impaired at baseline had a higher likelihood of becoming unemployed [283]. However, the relationship between adverse socioeconomic status and frailty, as demonstrated by unemployment and financial insecurity, may be mediated via a number of mechanisms including sustained psychosocial stress, inflammation, decreased physical activity, and adverse nutritional status [279].

4.4.6 HIV factors, cART and frailty

In multivariable analysis, no HIV factor apart from current protease inhibitor (PI) use was associated with frailty, with an approximate doubling of risk. Onen et al. showed a significantly higher PI use amongst frail individuals but did not examine the association further [180]. They also demonstrated a lower NNRTI use in the frail group. We examined the NNRTI efavirenz only, showing a significantly lower current usage amongst frail individuals (p=0.006) and some evidence of lower frailty in multivariable analysis (p=0.051). The relationship between these specific ART classes or drugs may be more complex however when you examine their recommended uses in relation to UK national treatment guidance [45]. Though PIs may be utilised as the third agent in standard ART regimes, they are also recommended for drug switching where a patient experiences virological failure or emergent resistance on their current ART regimen. Therefore, it may be that some of those on PIs have complex treatment histories, potentially experiencing episodes of viraemia which may drive chronic inflammation, acting as a substrate for frailty. Alternatively, PIs are associated with adverse effects including alterations in body composition and metabolic changes such as dyslipidaemia, insulin resistance and endothelial dysfunction [284–286], which may contribute to the overall loss of physiological reserve that heralds frailty. The protective nature of efavirenz could be attributed to patient selection in line with guidance recommending its avoidance in those with neurocognitive impairment or psychiatric comorbidity including active depression [45]. Given the strong relationship with mood disorder and frailty, the perceived protective effect may be due to the relative contraindication in these individuals rather than any intrinsic drug effect, though this may warrant further investigation.

In descriptive analysis, the only statistically significant HIV factor to be associated with frailty was a lower nadir CD4 count and despite no difference in current mean CD4 there was trend towards higher proportion of frail individuals with current mean CD4 <350 in our cohort with a borderline association with frailty in multivariable analysis (p=0.06). A low CD4, often taken as a CD4 count of <350 representing the traditional point at which cART was advocated, has been the most commonly replicated predictor of frailty across the HIV studies [10,166,175]. However, ours is a well-treated cohort with only 28 participants having CD4 counts below this level, which may explain the lack of association. Others have utilised even lower CD4 categories, particularly when investigating well treated cohorts such as Erlandson et al. who demonstrated that a current CD4 count <200 was the only HIV factor that predicted frailty [178]. In the South African study by Pathai et al., they found that for those people on cART, a CD4 count <500 was associated with an almost 3-fold increase in frailty risk (aOR 2.84; 95% CI 1.02-7.92), again seeing no relationship with any other HIV parameters [181]. As we move towards earlier initiation of ART at higher CD4 counts there will be interest in identifying CD4 thresholds at which the potential for frailty and other age-related comorbidities is at its lowest.

Though not significant, we demonstrate that those with frailty had been diagnosed with HIV for longer; were slightly younger at diagnosis; less likely to have been diagnosed late, and had been on ART for a longer duration. This may suggest that frailty is related to ageing in the presence of HIV rather than seen in those that are older at the time of diagnosis, though we have no longitudinal data to support this. The ASTRA study demonstrated that a longer duration of diagnosed HIV was associated with higher levels of self-reported symptomology, with higher prevalence of depression, anxiety and functional deficits, which apart from functional decline, was not observed with increasing age [259]. Work by Guaraldi et al. may corroborate this notion further, as they examined NICM and multimorbidity in those diagnosed at younger ages and therefore ageing with HIV (duration seropositive ≥20.6 years) compared to those with duration <11.6 years representing seroconversion at older age showing that multimorbidity and certain comorbidities were higher in those ageing with HIV, with multimorbidity

significantly higher in this group when restricted to those aged over 45 [89]. Lastly, Liu et al. showed that absolute telomere length to be shorter in those with HIV on cART compared to an HIV-negative cohort, with lower nadir CD4, longer HIV duration but not current low CD4 or detectable VL associated with shorter telomeres [287]. Additionally, though telomeres were shorter at older ages the slope of telomere decline with age was the same irrespective of HIV status, suggesting that this marker of biological ageing may be related to greater degrees of immunosuppression and may be ameliorated by cART [287].

It should be noted that data availability on whether a diagnosis was considered late was limited, meaning that there may have been misclassification in favour of timely diagnosis in our study, therefore underestimating any true effect. Additionally, though we can report on the duration of diagnosed HIV, we cannot make any comment as to how long the individuals have actually been living with HIV as we have no data on likely date of seroconversion.

It is possible, in high-income settings at least, that as HIV-positive populations become more treatment experienced, especially in the context of modern effective antiretrovirals with proactive early treatment, we may be seeing an improvement in HIV and immune parameters, reflecting less 'active' immune dysfunction. As such, these markers may be becoming less important as predictors of frailty and potentially other age-related comorbidities, being overtaken by more traditional risk factors such as age, depression and social disadvantage as described.

4.4.7 Symptoms of mood disorder and frailty

We have shown that the presence of symptoms of mood disorder, be that anxiety or depression was an important correlate of frailty, with a one-point increase in the HADS score associated with a 17% increase in the odds of frailty. Additionally, in univariate analysis, symptoms of anxiety and depression were both individually associated with frailty as was a pre-existing diagnosis of depression.

Psychiatric diagnoses, particularly depression were common and significantly associated with frailty in PLWH across a number of published studies [175,176,178–

[180,190]. The AGEhIV study authors describe how depressive symptoms were significantly higher in those with HIV, with symptoms suggestive of major depression, based on CES-D score, predicting higher frailty states [190]. In the cohort of IDU experienced individuals with and without HIV depressive symptoms were associated with a 2 and 4.4-fold increased risk of prefrailty and frailty respectively [175], and in the longitudinal MACS, the presence of depression was the strongest predictor of conversion to frailty (aOR 3.17; 95% CI 2.35-4.3) [176].

Depression is common in PLWH with prevalence of major depressive disorder reported to range from 20-37%, which may reflect complex psychosocial issues that can surround those with HIV such as stigma, social disadvantage or poor health status that may contribute to, or even mimic the symptoms of depression [288]. Depression in older adults without HIV (≥65 years) is reported to be lower with a global prevalence of major depression of 1-5%, which increases to around 10-15% for all depressive disorders [289]. The ASTRA study showed a prevalence of depression of 27.1% based on the Patient Health Questionnaire (PHQ-9) and 21.9% for anxiety using the Generalised Anxiety Disorder assessment (GAD-7), finding that anxiety and depression prevalence decreased with age (≥60 versus <60 years) but increased with duration of diagnosed HIV [259], though this age-related decline in depression prevalence was not seen in another study [290]. They also demonstrated that with age somatic symptoms of depression were reported more commonly than psychological ones as seen in younger individuals [259].

Frailty and depression have been shown to represent distinct yet highly overlapping entities [291,292]. This may be due to several factors. Firstly, there may be commonalities in symptomatology particularly those driving rule-based frailty identification as in the frailty phenotype such as exhaustion, low activity and weight loss. Secondly, they may share a common pathophysiology with potential causes being cerebrovascular disease, chronic inflammation, dysregulation of the hypothalamic-pituitary-adrenal axis or accelerated cellular ageing [289,293]. Lastly is the possibility that depression causes frailty or vice versa; though it should be stressed that most data in this area is observational with paucity of longitudinal studies [291]. It is important to consider their coexistence as there is

some evidence to suggest that the combination of frailty and depression may increase the risk of adverse outcomes, particularly in older women [294].

Mezuk et al. performed a narrative review of the literature pertaining to frailty and depression in later life. They demonstrated heterogeneity in the tools used to measure both depression and frailty, which more often focussed on functional ability using ADL limitation rather than formal frailty assessment. However, there was evidence to support a relationship between depression and frailty whether depression was assessed as a determinant or a consequence of the 'frailty' measure, suggesting a potential bidirectional relationship [291]. This work has been followed by a systematic review from Vaughan et al., which set stricter inclusion criteria around frailty (Fried phenotype) and validated depression assessment tools. In their chosen age group of adults ≥55 they identified 14 appropriate studies where the baseline prevalence ranged from 2.5-21.1% for frailty, 6.5-25.3% for depression and 16.4-53.8% for coexistent frailty and depression [293]. In cross-sectional studies, depressive symptoms were associated with increased odds of frailty but not prefrailty, with OR ranging from 1.8-4.3. In the included longitudinal studies, depressive symptomatology and use of antidepressants at baseline were associated with an increased risk of incident frailty and prefrailty. Additionally, baseline frailty was associated with incident onset of depression, with the former depression to frailty relationship appearing more robust in analyses according to the authors of the review [293]. However, this lends weight to the likely bidirectional relationship between frailty and depression.

Collard and colleagues looked at the relationship between depression, based on DSM-IV criteria, somatic comorbidities and frailty defined using an adapted frailty phenotype in a population of Dutch older adults with mean age 70.9 years. They demonstrated that frailty prevalence was significantly higher in those with depression than those without at 27% and 9% respectively [295]. Additionally, frailty and depression were both associated with comorbidity independent of each other, suggesting the presence of both shared and unique pathways with comorbidity. Frailty criteria appeared to matter, with the presence of exhaustion explaining most of the moderating effect of frailty in the relationship between depression and comorbidity. However, slow walking speed proved to be a

predictor of comorbidity independent of depression [295]. Where the relationship between frailty and depression has been examined, the presence of frailty was associated with more severe depressive symptoms or depression with primarily somatic symptoms, with particular concordance with exhaustion [296]. Additionally, frailty remained associated with depression when it was operationalised to avoid overlap with depressive symptoms, such as using grip strength and slow walk [297], and when using biological, purely functional or frailty index models [298].

Studies have examined the utility of different depression screening tools in PLWH, primarily to evaluate the best way of differentiating whether somatic symptoms are related to mood disorder, HIV or other coexistent comorbidities. None has emerged as a gold standard, with a paper advocating that tools should be chosen in line with research question and population under study [288]. As such, the HADS used here, focuses on the psychological symptoms of depression and anxiety, excluding somatic symptoms, which therefore may have minimised any over estimation of mood disorder or clear overlap with frailty parameters. The converse argument may be that older adults, as seen in ASTRA, tend to present more commonly with the somatic features of depression, which if unreported here may lead to underestimation, however the relative lower numbers of individuals aged over 65 in this study makes this less likely.

There is a paucity of literature around the association of frailty and anxiety. A Mexican study of adults over 70 showed that in those with anxiety, as assessed by a HADS-A score ≥8, frailty was significantly higher than those without (26.0 versus 11.4%, $p<0.01$). The presence of anxiety increased the odds of frailty and prefrailty by 2.3 times in multivariable analysis [299]. This is supported by findings of an Irish study using similar methodology, where anxiety was associated with a 4.3-times increased odds of frailty [300].

Research continues to debate whether depression should be considered a cause, comorbidity, confounder or consequence or even a combination of these in the context of frailty [289], however it cannot be ignored and the relationship warrants this level of investigation and is currently largely missing from frailty identification tools.

4.4.8 The role of functional parameters:

All included functional parameters were significantly associated with frailty. There were low rates of functional limitation in terms of mobility, falls or ADL disability in the non-frail group, whereas around 40% of frail participants describe at least one ADL disability, which increased to 75% of frail individuals falling in the last year and 90% reporting mobility problems. Functional issues have not been examined widely in the HIV and frailty literature but in support of our findings Erlandson et al. report significantly higher self-reported pain and falls in the frail compared to non-frail groups [97]. Greene et al. investigated the prevalence of certain geriatric syndromes in a group of older PLWH in San Francisco, showing that 25.8% had fallen, 25.2% reported difficulty with one or more personal ADLs and 46.5% reported difficulty with instrumental ADLs [4], and lastly in a small Boston-based study of 50 HIV+ adults aged over 45, 88% of those with frailty describe limitation in more than five ADLs [189].

Though not specifically focussed on frailty, the ASTRA study showed significant and independent increases in functional disorders with both increasing age and duration of HIV with 38.1% reporting functional problems, 27.1% for mobility and 12.3% for self-care [259]. Our findings are comparable if not higher, which again may reflect the higher age of the cohort. Lastly, in two cohorts with mixed HIV serostatus there was no significant difference in the prevalence of impaired physical functioning between those with and without HIV, and although functional impairment increased with age in both groups, medical comorbidity was the best predictor [265,301].

Fried et al. describe that though frailty, comorbidity and disability are interlinked, and often overlapping in the same individual, they remain distinct entities [276]. This was demonstrated in the Cardiovascular Health Study where one could have each of these alone, all three or two in any combination [9]. The interconnectedness of these concepts makes it difficult to ascertain whether functional impairment or disability occurs in parallel with or has a cause/consequence relationship with frailty, which was also seen in context of depression. We cannot comment on the direction of the observed relationship due to our cross-sectional design.

It has been demonstrated that frailty, however measured, is a risk factor for functional decline and falls [9,302,303], but one can also theorise that functional impairment could limit physical activity, interfere with gaining adequate nutrition, and negatively affect ability to self-manage any medical comorbidity or risk factors that could ultimately lead to frailty [276]. It is therefore essential to recognise that functional impairment may precede frailty and represent an opportunity to intervene to prevent its occurrence/progression and further functional decline. Ultimately an awareness of the interaction between frailty, disability, comorbidity, and as discussed depression are vital in delineating the needs of individual patients to provide holistic care.

The fact that all of the chosen functional parameters are both more prevalent in those with frailty and their presence increased the odds of its occurrence in multivariable analysis make them potentially useful as points of enquiry in clinical review. Where present they may alert the clinician to the possibility of underlying frailty or risk of frailty that could warrant further investigation and management. However, the utility in this respect would need to be assessed in longitudinal work.

4.4.9 Strengths and limitations

This study solely focuses on those considered older with HIV representing the oldest cohort reported on to our knowledge. The age range extends to 87 years old and encompasses a spectrum of individuals ageing in the presence of HIV. We describe a well-treated cohort representative of the UK-picture and potentially many other settings with good access to ART, particularly for MSMs with HIV.

We have utilised a standardised approach to frailty assessment in the form of the adapted frailty phenotype that makes use of the objective measures of grip strength and walking speed. This approach has been used in the setting of HIV since some of the earliest work by Onen et al. [180]. Additionally, frailty was assessed prospectively without reliance on retrospective data or recall. Lastly there was full ascertainment of frailty status for all participants.

The comprehensive nature of the assessment, designed to be akin to a comprehensive geriatric assessment, allows us to comment on predictors across

biological, psychological and social parameters, the latter of which have been broadly neglected in frailty assessment methods to date.

Our cohort was smaller than our recruitment target of 300 meaning that the precision around the frailty prevalence is wider than we hoped to estimate. However, the achieved sample size is comparable to that seen in the systematic review on the subject where the mean size of HIV study population (outside of the US national MACS) was 327, ranging from 41-1206 [10].

Though frailty prevalence was higher than expected at 19%, this represents only 48 participants which restricted the number of parameters that could be included in any multivariable model without losing statistical power and as such we cannot exclude the role of residual confounding. This is particularly relevant with respect to those factors not included in the core model. This included HIV factors though they were explored at model design stage, especially CD4 count <350, which did not strengthen the model whereas comorbidity count and HADS score did. The small number of frail individuals also means that some of the associations presented have wide confidence intervals around the calculated odds ratios, which may make these findings less secure, however the suggestion of relationship may warrant further examination in larger populations.

We attempted to recruit a study population that was representative of the current UK demographic of HIV-positive older adults. However, we were unable to recruit the planned number of women and those of black African ethnicity. The final cohort was 91% male, with the clear majority being white MSMs. Therefore, although the findings presented are representative of the South-East coast HIV demographic, they may not be generalisable to the wider HIV-positive population, especially with respect to women and those of non-white ethnicity. Additionally, it must be noted that we are reporting on a treatment experienced cohort with good HIV control, which does reflect the UK picture, however different predictors may be seen in those with less well controlled HIV, such as in resource-poor settings.

Although we used a standardised and widely utilised modified frailty phenotype with proven construct validity [180], this is still a variant of the original Cardiovascular Health Study phenotype described by Fried et al. [9]. Therefore, it

may have led to some misclassification, with potential to have overestimated prefrailty and frailty due in part to the modification of the low activity parameter as discussed. We may have seen a more modest frailty prevalence had we used a more objective tool, though the prevalence remains comparable to those studies that have employed this method [175,181,190].

We used consecutive rather than random sampling during participant recruitment that has the possibility of introducing selection bias. However, we were mindful to ensure consecutive invitation of all eligible participants to minimise this risk and given that recruitment ran over a one-year period then the assumption is that each person would have been informed of the study at least once. Most participants were recruited from the Brighton HIV clinic which does operate a remote follow-up service conducted via email and telephone, which potentially may be utilised more readily by fitter individuals who may find attending the clinic in person difficult due to work commitments or who potentially have less complex problems. It is possible that these individuals may not have been informed of the study and as such if due to this or the fact that fitter individuals who are in full time employment *et cetera* did not participate then we may have overestimated frailty. This could also have occurred if those with the most concern about their current health, physical functioning and issues of ageing had preferentially opted to join the study but this is less likely given the spectrum of participants presented. It is also feasible that the most unwell or functionally impaired may have found it more difficult to attend an additional research visit which could have led to an underestimation in frailty prevalence.

The cross-sectional design limits our ability in making any conclusions regarding causality of the presented frailty predictors. As discussed, it is possible that some of the factors may have a bidirectional relationship with frailty being potentially both cause and effect, as in the example of depression. Here, low mood may cause reduction in energy, motivation, reduced physical activity which may lead to physical deconditioning which ultimately results in reduced muscle strength and slow walking, and thus frailty. Alternatively, changes in health and functional status secondary to one's frailty state may lead to a negative alteration in mood as a consequence.

4.5 Conclusion

We have described a high prevalence of frailty in this cohort of older adults with HIV, which exceeds that seen in those without HIV at older ages. The presence of medical comorbidity and symptoms of mood disorder are strong correlates of frailty as is age to a lesser degree. HIV-factors do not appear to be associated specifically with frailty, which may suggest that in the current era of HIV care, though frailty may be occurring prematurely it appears to be driven preferentially by traditional age-related frailty predictors that are more prevalent than in HIV-negative cohorts.

Chapter 5 - Biological determinants of frailty

5.0 Chapter overview

Frailty is described as a biological syndrome, with emphasis placed on declining physiology across a number of body systems, which may present clinically as the phenotypic frailty traits previously described by Fried et al. [9]. Taking one step back from this, Ferrucci et al. consider four core domains that contribute to physiological ageing, which are alteration in body composition, imbalance in energy supply and demand, homeostatic dysregulation and neurodegeneration [304]. Dysfunction in these, particularly in combination, may lead to the development of frailty and in turn the manifestation of geriatric syndromes.

These concepts can be summarised theoretically as a cycle of frailty, which was characterised by Fried et al. in 1998, acting as a precursor for determining the core components that ultimately went on to form the frailty phenotype. Figure 5.1 shows this cycle, demonstrating that nutritional deficiency contributes to body composition alteration in the form of unintentional weight loss and sarcopenia (loss of muscle mass) with consequent negative alterations in metabolic state (reduced VO_2 max and basal metabolic rate) and functional ability with reduced muscle strength and slower walking speed. These culminate in reduced physical activity and ultimately decreased total energy usage (or predominant expenditure of available energy on fundamental activities of daily living), which drive further cycles of physiological and functional decline [9,305].

This cycle of frailty introduces some important biological processes that may contribute towards the development of frailty, namely nutritional deficit, loss of muscle mass or sarcopenia, and reduced physical activity. The validity of their contribution to frailty can be demonstrated by a review of ongoing and registered RCTs in people with frailty, where over half are investigating the role of exercise and/or nutritional interventions [306]. Lastly, more recent work has focussed on the biological contribution that inflammation plays in the development of frailty [307]. This chapter will seek to explore these factors in the context of our HIV-positive cohort.

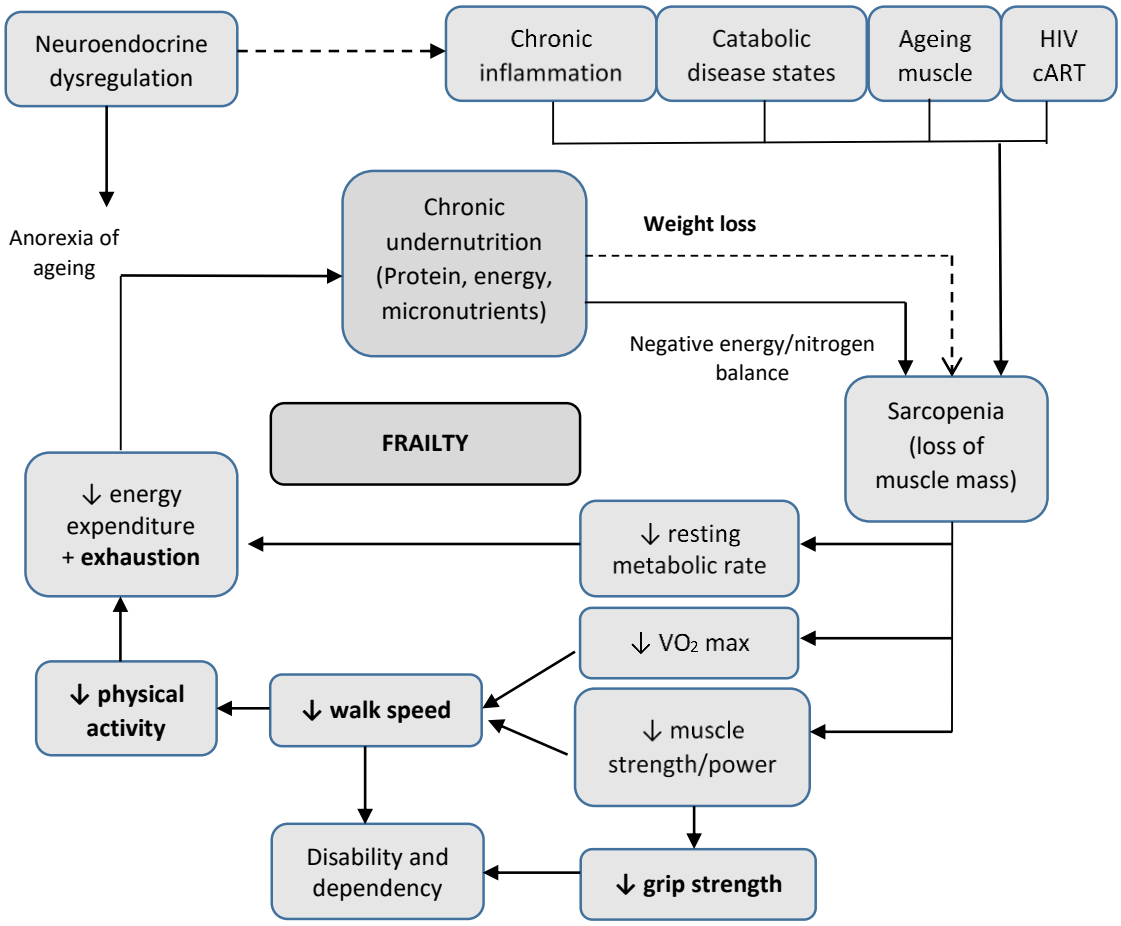


Figure 5.1: Proposed cycle of biological contributors to the frail state, adapted from Fried et al. [9]

Chapter aims

This chapter aims to investigate some of the biological predictors of frailty as described in the theoretical cycle of frailty through the examination of body composition, nutrition, physical activity and blood-based biomarkers within our cohort.

We therefore aim:

- To describe the patterns of body composition seen within the cohort and assess any relationships with frailty.
- To formally assess for the prevalence of sarcopenia and presarcopenia using DXA and anthropometric measures.
- To describe any relationship between frailty and sarcopenia.

- To describe the nutritional intake for the cohort based on food frequency data, examining the effect of nutrition on frailty.
- To describe the relationship between physical activity and frailty.
- To describe the relationship between routine laboratory blood parameters and frailty status.
- To describe levels of inflammation within the cohort and any association of a pro-inflammatory state with frailty.

We hypothesise that those with frailty will demonstrate more adverse markers of body composition, higher prevalence of sarcopenia, poorer nutritional intake and higher inflammatory markers when compared to non-frail individuals

5.1 Body composition and sarcopenia

5.1.1 Introduction

Natural ageing is associated with negative changes to body composition, particularly with respect to muscle where there is an estimated loss of between 30-50% of skeletal muscle mass occurring between the ages of 40 and 80 years [308]. Various studies have been consistent in demonstrating trends in altered body composition with age, showing declines in lean mass (alternatively termed fat free mass), increases in fat mass and general decrease in weight in later older age that may be due preferentially to loss of muscle mass [309–312]. These alterations have been linked to reduced physical functioning [312,313] and predominantly in men, impaired mobility [314] and falls [313].

Loss of muscle mass contributes to sarcopenia. Like frailty, sarcopenia lacks an international consensus definition; however a European working group on sarcopenia in older people (EWGSOP) was convened in 2009. They defined sarcopenia as a syndrome of progressive and generalised loss of both skeletal muscle mass and strength, which is associated with a risk of adverse outcomes [315]. There is emphasis placed on the combination of both reduced mass and function, as assessed by declines in strength (for example grip) or performance (such as slow walking speed), with an isolated reduction in muscle mass representing a pre-sarcopenic state. The EWGSOP recommend the use of grip

strength as the measure of weakness and a defined slow walking speed for muscle performance [315].

A meta-analysis by Cooper et al. investigated the effect of grip strength on all cause mortally, which included individuals under 60 years old. They showed that those with the weakest grip (lowest compared to highest quartile) had a 67% increased risk of mortality (Hazard ratio (HR) 1.67; 95% CI 4.45-1.93) after controlling for age, gender and body type [316]. They also demonstrated a protective effect of stronger grip, with a 3% reduction in mortality risk for every 1kg increase in grip strength (HR 0.97; 95% CI 0.96-0.98). Similar results were observed when analyses were restricted to those under 60 years old [316], which is in keeping with UK normative grip strength data, where following achievement of peak grip strength, declines start as early as the fifth decade of life [317]. A further meta-analysis showed a survival advantage associated with increasing gait speed, with a HR for mortality of 0.88 per 0.1m/s increase in speed (95% CI 0.87-0.90). Gait speed was also shown to be a good predictor of 5- and 10-year mortality [318]. Cooper's work also confirmed this association, however unlike with grip strength, population data on the effect of walking speed on mortality in younger individuals is lacking [316]

A number of mechanisms may promote sarcopenia including an imbalance of protein synthesis and breakdown, disruption in neuromuscular integrity and increased muscle fat content [315]. The cause of sarcopenia is likely multifactorial in most older adults, with contributions from immobilisation and disuse, neurodegenerative disease, vascular disease, other chronic disease states, especially endocrine conditions, chronic inflammation and overt nutritional deficiency [319].

The European working group recommend CT or MRI as the gold standard research tools for accurately assessing muscle mass and body composition, however they recognise the practical limitations, suggesting Dual-energy X-ray absorptiometry (DXA) as the preferred alternative for clinical and research purposes [315]. Another alternative is to assess sarcopenia through use of anthropometric measurements, such as using skinfold thickness to calculate fat free mass, which showed good correlation with that measured on DXA (r=0.91)

[320]. Additionally, Landi et al. used the lowest tertile of mid-arm muscle circumference (MAMC) as a proxy for sarcopenia, which predicted poor functional performance in a group aged over 80, however they had no imaging modality for comparison [321]. Lastly mid-calf circumference (of <31cm) has been used, showing good predictive ability for disability but poor for sarcopenia when compared with DXA [322]

Body composition changes in HIV

Alterations in body composition have been widely documented and researched in PLWH. Emphasis has been placed on issues such as wasting and weight loss associated with advanced HIV-infection, particularly in the pre-ART era; and since cART introduction on the adverse effects associated with their use, including premature reductions in bone mineral density [80]. Body fat distribution has also warranted attention due to lipodystrophy secondary to ART, especially early NRTIs [323]. Lipodystrophy has been divided into lipoatrophy, characterised by a loss of peripheral subcutaneous adipose tissue and lipohypertrophy, where truncal and visceral fat increase, which have been demonstrated on imaging, even in the absence of a prior clinical diagnosis [324]. In addition to the recognised associations of lipodystrophy of dyslipidaemia, insulin resistance, metabolic syndrome and inflammation, it has been found to predict low grip strength [325] and has been linked to decreased health-related quality of life [326,327].

Adverse body composition has been examined in the context of HIV with the AGEhIV study showing a significant association between low BMI and high waist-to-hip ratio with frailty, speculating a potential role for lipodystrophy [190]. Conversely a longitudinal Finnish population study with mean follow-up of 22-years demonstrated that being overweight or obese by BMI measurement was associated with a significantly elevated odds of incident frailty in later life even after adjusting for age, physical activity, alcohol use and chronic disease [328]. This suggests there may be a complex relationship with frailty and body mass or a differential response in those with and without HIV.

Muscle-related changes have received less attention, particularly with respect to the formal assessment of sarcopenia, however this is gaining interest as age-related problems in PLWH increase in priority for patients, clinicians and

researchers. Wasserman et al. conducted a cross-sectional study of 80 virally-suppressed participants aged over 45 using the EWGSOP approach to assess for sarcopenia, using body impedance analysis to assess muscle mass. They showed that skeletal muscle mass decreased with increasing age and found a prevalence of 5% for sarcopenia and 20% for presarcopenia. Sarcopenia was associated with older age, shorter HIV duration and lower nadir and current CD4 [329]. A similar approach was taken in a study in Brazil, comparing PLWH aged over 50 to HIV-negative controls aged over 60. Those with HIV had higher levels of sarcopenia than those without (24.2% versus 6.7%), with HIV associated with five times the risk of sarcopenia after controlling for age and BMI (aOR 5.20; 95% CI 1.40-19.20) [330]. Other studies defined sarcopenia based on low muscle mass only, omitting assessment of low strength or slow walk. Erlandson et al. showed a 35% prevalence of low muscle mass that was associated with low physical functioning, which in turn was associated with lower BMI and increased fat mass [331]. Another found low muscle mass in 21.9% in a male group (median age 42), which showed overlap with low bone density and to a lesser extent lipodystrophy [332].

Most research has been cross-sectional, however Yarasheski et al. examined muscle mass at two time points 5-years apart using MRI techniques in PLWH and a population control group showing that HIV-positive men had significantly lower muscle mass at baseline and at 5-years compared to HIV-negative men, with no such difference seen in women. Overall however there was no difference in change in muscle mass between those with and without HIV, suggesting no faster decline, though the mean age here was 43, which is before peak muscle loss occurs. They did find that age was associated with skeletal muscle loss and that higher CD4 and increased physical activity were protective against loss in those with HIV [333].

Declines in muscle mass and strength may contribute to functional and walking disability making it an integral part in assessing age-related outcomes in PLWH. Additionally, it may have more severe consequences as shown by Scherzer et al. in the US-based Fat Redistribution and Metabolic Change in HIV study (FRAM) [247]. Here, 922 HIV-positive individuals of median age 43 years were

followed-up for 5-years after original body composition assessment using MRI and mid-upper arm circumference. They demonstrated that being in the lowest tertile of skeletal limb mass in the arm or leg was independently associated with 5-year mortality, as was the case for the highest tertile of visceral adipose tissue [247].

Section aims:

In this section, we aim to describe the patterns of body composition seen within the cohort and assess any relationships with frailty status. We will also aim to describe the prevalence of sarcopenia and presarcopenia using DXA and anthropometric measures, and lastly to describe any relationship between frailty and sarcopenia.

5.1.2 Methods

Comprehensive methodology of the study has been provided in chapter 3. Apart from the DXA sub-study and those with missing data, the full cohort (n=253) have been included in each of the investigations discussed throughout this chapter.

Sarcopenia

DXA scanning

All participants classified as frail (n=48) were invited to attend for a whole body DXA scan at the Clinical Research and Investigation Unit, Royal Sussex County Hospital Brighton. For each frail individual undergoing DXA scanning we consecutively invited the next pre-frail and robust participants of the same gender aged within a 5-year age range to aid comparability, aiming for two non-frail individuals for every one frail. The final DXA subgroup consisted of 108 participants, 31 frail, 44 prefrail, and 33 robust. As frailty diagnosis occurred in random order, selection bias was minimised by taking a consecutive invitation approach.

Body composition was evaluated using whole body DXA (or half-body, with adjustment, for those too large to be accommodated by the DXA table), using a GE full-body iDEXA with Lunar iDXA software version 11.40.004. Estimations of both whole body and regional (trunk and appendicular) lean mass and fat mass (+ percentage) were calculated.

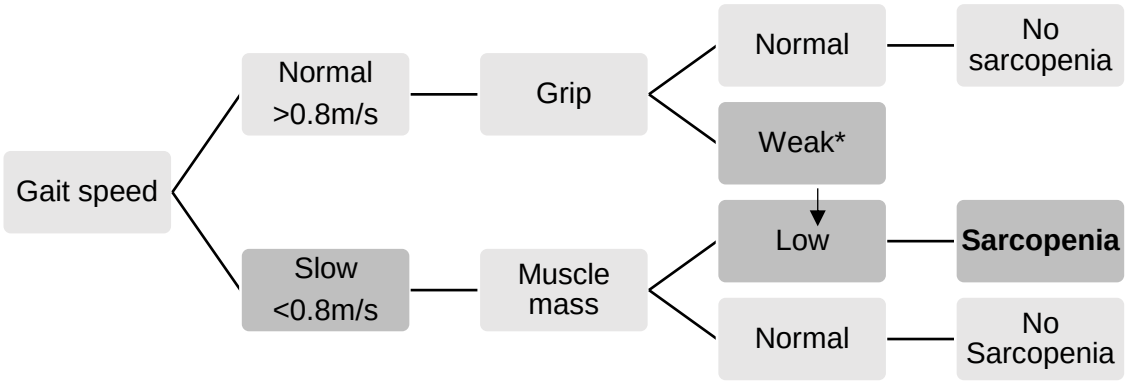
All DXA scans were performed to the same procedure, with patient supine, arms at, but not touching sides of body with palms facing the thighs with thumbs positioned upwards. Participants were scanned wearing a hospital gown. The same scanner was used for all participants with radiographers performing the DXA scans blinded to the frailty status of the participant. Prior to enrolment and as part of the consent process, participants were made aware of the minimal associated dose of ionising radiation (less than a standard chest X-ray) and were fully aware that the scan was an optional component of the study, as described in the participant information sheet (as shown in Appendix 2: Ethics Approvals Documents, Patient Information Sheets, Consent Forms).

Sarcopenia based on DXA parameters

Sarcopenia was calculated using the algorithm of the EWGSOP as shown in Figure 5.2 [315]. Muscle mass was calculated using DXA derived calculation of the skeletal mass index (SKI), which is a product of the appendicular skeletal muscle mass (sum of limb lean muscle mass) over height squared. Cut-offs were taken from work by Baumgartner et al., where using two standard deviations below the gender-specific young adult mean, SKI values of less than 5.45kg/m^2 for women and 7.26kg/m^2 for men represented low muscle mass [313]. Walking speed was considered slow if ≤0.8m/second (derived from the timed walk as part of the frailty assessment) and an abnormal grip strength, was taken as those scoring as weak on the frailty phenotype grip strength assessment, which as described used gender and BMI cut-offs.

Sarcopenia was considered as present or absent based on the above definitions and further categorised into three accepted groupings of pre-sarcopenia (low muscle mass only), sarcopenia (low mass and reduced grip or speed) or severe sarcopenia (low muscle mass and weak grip and slow speed) [315], which were compared to the reference group of normal muscle mass.

Sarcopenic obesity was defined as sarcopenia by the above measures in addition to a total body fat mass >30% in women and >40% in men [314]



* Measure muscle mass if weak grip

Figure 5.2: EWGSOP algorithm for ascertaining sarcopenia

Sarcopenia based on anthropometric parameters

Sarcopenia was also evaluated in two additional ways in the full cohort using anthropometric data:

Skinfold thickness method:

Skinfold measurements (in mm) were collected from four body sites, triceps, subscapular, suprailiac and mid-thigh, as described in chapter 3. The means of each were summed and the logarithm taken (L). This was then used in the Durnin and Womersley equation to calculate body fat density (D), using the respective equations below for males and females aged over 50:

- Males: D=1.1715 - (0.0779 x L)
- Females: D=1.1339 – (0.0645 x L)

The above D values were used to calculate an estimated body fat percentage using the Siri formula, and then on to get the fat free mass (in kg) from the measured body weight (in kg):

- % body fat= (495/D) – 450
- Fat mass (FM)= body weight x % body fat

- Fat free mass (FFM)= body weight – FM

The bottom third were considered to have low muscle mass. The FFM calculated via this method was correlated against DXA derived values for those that have them [320].

Mid-limb measurements:

Mid-arm muscle circumference (MAMC) was calculated using the mid-arm circumference and triceps skinfold measurements, taken in duplicate with mean values used as described in chapter 3. The following formula was applied[321]:

- MAMC= mid-arm circumference – (3.14 x mean triceps skinfold thickness)

Mid-calf circumference (MCC) was used with a cut-off of <31cm indicating low muscle mass [322]

Statistical considerations

Throughout this chapter all variables were assessed for normality. Descriptive statistics will be presented as frequencies with corresponding percentages for categorical data. Continuous data was paired with mean and standard deviation for normally distributed data and median and interquartile range if skewed.

Factors potentially associated with frailty were analysed as described in chapter 4, with core analyses comparing frail to non-frail (pre-frail plus robust participants) individuals using chi-squared tests (categorical data), unpaired two-sided t-tests (normally distributed continuous data) and Mann-Whitney U test (non-normally continuous data) where appropriate. Associations with frailty were assessed using univariate and multivariable logistic regression to obtain OR for any association, presented with its 95% confidence interval and p-value. Continuous data was, where appropriate, grouped by accepted cut-offs or into percentiles. Where tests for linear trend were satisfied, grouped variables were entered into models as a continuous variable, modelling change in outcome per percentile increase in the independent variable. The multivariable model created in chapter 4 was used unless otherwise stated. For some analyses, it was not possible to use the full model due to multi-level categorical data, missing data reducing frailty

events or where different adjusting parameters were more appropriate. These will be described where used.

Certain parameters were explored across the three frailty groups (robust, prefrail, frail), using chi-squared tests (categorical data), one-way ANOVA (normally distributed continuous data) or Kruskal-Wallis test (non-normally continuous data) where appropriate and where relevant assumptions have been met. Where these tests were significant pairwise examinations were made. As such, Bonferroni correction was applied to account for multiple comparisons made when assessing the three levels of frailty of robust, pre-frail and frail in the groupings of robust vs. prefrail, pre-frail vs frail and robust vs. frail. Here, to preserve the type I error rate, statistical significance required $p<0.017$.

Correlations were made using Pearson's (r) test for normally distributed values and Spearman's rank (ρ) for skewed and ordinal data. For all tests significance will be taken at the 95% with p-values <0.05. All analyses were performed in Stata version 13.

This analysis approach has been utilised across this whole chapter and will not be described further unless additional tests or an alternative methodology has been employed.

5.1.3 Results

Sarcopenia

108 (42.7%) participants underwent DXA scanning to assess body composition and for the presence of sarcopenia. Table 5.1 shows the demographics between those with and without DXA scanning. As planned, there was a significantly higher representation of frail individuals in the DXA subgroup with 64.6% (31/48) compared to 37.6% (77/205) of non-frail individuals ($p=0.002$), and the two non-frail to each frail subject ratio was achieved. To break this down further, of those without frailty receiving a DXA scan (n=77) 44 were prefrail and 33 robust, meaning a slightly higher representation of those with prefrailty. There were no significant differences in age, sex, current CD4 count or BMI between those with and without DXA scans. There was lower representation of non-white ethnicity in the DXA group (4.6% versus 11.7%). The median number of comorbidities per

group was two, however there were significantly higher levels of comorbidity overall in the scanned group (p<0.001).

Table 5.1: Group demographics by those with and without DXA scanning

	DXA n=108 (%)	No DXA n=145 (%)	p-value [a]
Age [b]	59.8 (55.9-64.3)	59.6 (54.8-66.4)	0.763
Female gender	7 (6.5)	16 (11.0)	0.213
Non-white ethnicity	5 (4.6)	17 (11.7)	**0.048**
BMI [c]	26.5 (5.0)	26.7 (3.8)	0.672
Current CD4 count [c]	652.2 (274.3)	660.6 (290.6)	0.815
Comorbidity count [b]	2 (1.5-3.5)	2 (1-3)	**<0.001**

[a] p-value based on Chi-squared test unless stated otherwise
[b] Median (IQR), p-value generated with MWU-test
[c] Mean (sd), p-value based on two-way t-test

Based on the EWGSOP definition 22/108 participants receiving DXA scanning met the criteria for sarcopenia, giving a prevalence of 20.4% (95% CI 13.7-29.2%). Of the full 108 scanned, just under half had a normal muscle mass at 49.1%. 33/108 (30.6%) had low muscle mass but no functional loss, making them presarcopenic and 6/108 (5.6%) had severe sarcopenia owing to functional deficits in walking speed and grip strength.

Table 5.2 shows the associations with sarcopenia (as compared to those with no sarcopenia) in the scanned subgroup. Those with sarcopenia were older, with mean age of 63.6 (p=0.03), and were all white males. Those with sarcopenia were significantly more likely to be out of work or formally retired (95.5% versus 62.8%; p=0.003), however there was no difference in financial security or years in education. Furthermore, no differences were seen in behavioural risk factor of smoking, alcohol or drug use. Those with sarcopenia had a significantly lower mean body weight and body mass index compared to those without.

Sarcopenic participants were significantly older at diagnosis with mean age of 47.6 years compared to 42.5 years (p=0.042), with a non-significant trend towards a higher proportion being diagnosed over the age of 50 (40.9% versus 23.8%; p=0.095). Those with sarcopenia had HIV for a shorter duration (13.8

versus 18 years; p=0.397), had a statistically significantly lower CD4 nadir count at 110 compared to 174 in those without sarcopenia (p=0.032) and a borderline association with current CD4 below 350, as seen in 22.7% of those with sarcopenia and 8.1% of those without (p=0.05). Current mean CD4 count, CD4/8 ratio, prior AIDS diagnosis and exposures to protease inhibitors, zidovudine or d-drug NRTIs were not associated with sarcopenia in this group.

Sarcopenic individuals exhibited significantly higher numbers of comorbidity, but no significant difference in their number of non-antiretroviral medication use. They also had a higher HADS score (p=0.06), with significantly higher burden of moderate to severe symptoms of anxiety (45.5% versus 19.8%; p=0.013) and depression (27.3% versus 10.5%; p=0.042). Cognitive scores were lower in the sarcopenic individuals with a median score of 25, which is below the lower end of normal at 26 (p<0.001).

Those with sarcopenia reported significantly lower levels of physical activity and slower times to complete the timed get up and go and five times sit to stand tests. They reported higher levels of mobility problems, with a higher, yet not significant proportion reporting falls in the previous year. There were higher levels of impairment in activities of daily living in those with sarcopenia, but only statistically significantly so for instrumental over personal ADLs (p values of 0.001 and 0.065 respectively).

Table 5.2: Associations with sarcopenia based on DXA diagnosis

	All DEXA N=108 (%)	No Sarcopenia N=86 (%)	Sarcopenia N=22 (%)	p-value [a]
Demographics				
Age [b]	60.7 (7.04)	60.0 (6.55)	63.6 (7.04)	**0.031**
Female sex	7 (8.1)	7 (8.1)	0 (0.0)	0.166
Non-white ethnicity	5 (4.6)	5 (5.81)	0 (0.0)	0.247
Financial insecurity	41 (38.0)	32 (37.2)	9 (40.9)	0.750
Not working	75 (69.4)	54 (62.8)	21 (95.5)	**0.003**
Education [c]	12 (11-16)	13 (11-16)	11 (11-14)	0.138
Body composition				
BMI [c]	26.5 (5.00)	27.1 (5.14)	24.0 (3.40)	**0.008**
Weight (kg) [c]	80.3 (15.84)	82.6 (16.05)	71.5 (11.54)	**0.003**
HIV factors				
Age at diagnosis [b]	43.6 (10.6)	42.5 (9.97)	47.6 (12.01)	**0.042**
Diagnosis aged ≥50 [b]	29 (26.9)	20 (23.3)	9 (40.9)	0.095
HIV duration (years) [c]	17.4 (10.8-23.7)	18.0 (11.6-23.6)	13.8 (10.3-25.7)	0.397
CD4 count [c]	615 (443-864)	627 (460-907)	557 (411-711)	0.140
CD4 <350	12 (11.1)	7 (8.1)	5 (22.7)	0.052
CD4 nadir [c]	157 (83-212)	174 (90-228)	110 (38-192)	**0.032**
CD4/8 ratio [b]	0.70 (0.37)	0.72 (0.39)	0.62 (0.31)	0.240
AIDS diagnosis	37 (34.3)	26 (30.2)	11 (50.0)	0.081
Comorbidity				
Comorbidity count [c]	2 (1.5-3.5)	2 (1-3)	3 (2-5)	**0.015**
Non-ARV drugs [c]	4 (2-6)	3.5 (2-6)	4.5 (3-7)	0.126
HADS score [c]	13 (7-18)	12 (7-18)	16 (9-23)	0.063
Depression	15 (13.9)	9 (10.5)	6 (27.3)	**0.042**
Anxiety	27 (25.0)	17 (19.8)	10 (45.5)	**0.013**
MoCA [c]	27 (25.5-29)	28 (26-29)	25 (24-27)	**<0.001**
Functional parameters				
PASE score [c]	139 (92-197)	146 (108-207)	88 (73-131)	**0.002**
iADL disability	12 (11.1)	5 (5.8)	7 (31.8)	**0.001**
pADL disability	16 (14.8)	10 (11.6)	6 (27.3)	0.065
Mobility problem	41 (38.0)	27 (31.4)	14 (63.6)	**0.005**
Falls	44 (40.7)	32 (37.2)	12 (54.6)	0.140
TGUG time (secs) [c]	8.5 (7.2-11.3)	7.8 (7-9.4)	11.8 (9.9-13.9)	**<0.001**
5SST (secs) [c]	13.5 (11.5-17.5)	13.3 (10.9-16.5)	16.2 (13.3-22)	**0.009**
Mean grip (kg) [b]	34.8 (10.4)	36.9 (10.2)	26.7 (7.2)	**<0.001**

[a] p-value based on Chi-squared test unless stated otherwise

[b] Mean (sd), p-value based on two-way t-test

[c] Median (IQR), p-value generated with MWU-test

Table 5.3 shows the relationship between the three frailty categories and the classification based on muscle mass of normal, presarcopenic and sarcopenic. Around 50% of those in each frailty group had a normal muscle mass on DXA scanning. Presarcopenia decreased in prevalence as frailty state increased being present in 48.5%, 34.1% and 6.5% of those classified as robust, pre-frail and frail respectively. Sarcopenia was present in almost half of those with frailty (45.1%) and 18.2% with prefrailty. No-one in the robust group was sarcopenic.

Table 5.3: Relationship between frailty and sarcopenia in those with DXA scans

N=108	Robust	Prefrail	Frail
Normal muscle mass	17 (51.5)	21 (47.7)	15 (48.4)
Presarcopenia	16 (48.5)	15 (34.1)	2 (6.5)
Sarcopenia	0 (0.0)	8 (18.2)	14 (45.1)
Chi-squared test p <0.001			

Table 5.4 shows the distribution of frailty criteria by sarcopenia status. All the criteria were significantly more prevalent in those with sarcopenia compared to those without.

Table 5.4: Association between sarcopenia and the frailty phenotypic characteristics

Frailty criteria	No Sarcopenia (n=86)	Sarcopenia (n=22)	p-value [a]
Low physical activity	45 (52.3)	18 (81.8)	0.012
Exhaustion	34 (39.5)	16 (72.7)	0.005
Weight loss	8 (9.3)	7 (31.8)	0.006
Weak grip	17 (19.8)	14 (63.6)	<0.001
Slow walk	4 (4.7)	10 (45.5)	<0.001

[a] p-value based on Chi squared test

Sarcopenia was also assessed by calculating body composition using skinfold measurements as described. 222/253 (87.7%) had full skin-fold data, allowing categorisation of sarcopenia. 73 (32.9%) had low muscle mass, 53 (23.9%) had no functional deficit making them presarcopenic and 20 (9%) met the criteria for

sarcopenia, which is lower than the observed prevalence based on DXA findings (20.4%).

We saw very strong correlations between the fat free mass calculated via the skinfold method and the fat free mass ($r=0.83$, $p<0.001$) and appendicular skeletal muscle mass ($r=0.83$ $p<0.001$) gained from DXA scanning. The same was true of total fat mass gained from both methods ($\rho=0.88$, $p<0.001$).

Frailty and body composition

Body composition was assessed via anthropometric measurements and DXA scanning in a subgroup of individuals as described. Table 5.5 presents data available for the full cohort and divided by frail and non-frail participants. Data was available for the full cohort on weight, height, and hip and waist circumferences. There were no statistically significant differences in BMI but there was a trend towards difference in proportion with obesity, which was more common in those with frailty (31.3 versus 19%, $p=0.063$). The mean waist-to-hip ratio (WHR) was high in both groups, with no significant difference in proportions of those with WHR>1, indicative of abdominal obesity ($p=0.614$). We applied our multivariable model to these body composition parameters with full cohort data to assess for relationship with frailty. None of those described in Table 5.5 predicted frailty.

When examined across the three frailty groups (robust, prefrail, frail) there were no differences seen in weight or WHR. BMI increased with frailty state with mean BMI values of 25.6, 27.1 and 27.5 for robust, prefrail and frail groups respectively ($p=0.015$). Compared to the robust group, who had the lowest mean BMI, univariate analysis showed that a 1-unit increase in BMI was associated with a 10% increase in the odds if prefrailty (OR 1.10; 95% CI 1.02-1.18, $p=0.008$) and frailty (OR 1.10; 95% CI 1.02-1.20, $p=0.017$). However, there was no association for BMI between the prefrail and frail groups ($p=0.623$). A similar pattern was seen for obesity where the proportion of obese participants increased with higher frailty states at 11.7%, 25.2% and 31.3% from frail to robust. Obesity increased with frailty (OR 3.43; 95% CI 1.43-8.23, $p=0.006$) and prefrailty (OR 2.54; 95% CI 1.19-5.45, $p=0.016$) when compared to the robust group only.

Table 5.5: Body composition parameters by frailty status

	Full cohort N=253 (%)	Not frail N=205 (%)	Frail N=48 (%)	p-value [a]
BMI	26.6 (4.36)	26.4 (4.00)	27.5 (5.61)	0.120
Under weight	4 (1.6)	3 (1.5)	1 (2.1)	0.271
Normal weight	89 (35.2)	73 (35.6)	16 (33.3)	
Overweight	106 (41.9)	90 (43.9)	16 (33.3)	
Obese	54 (21.3)	39 (19.0)	15 (31.3)	
Weight (kg) [b]	80.6 (14.6)	80.5 (14.0)	81.4 (17.0)	0.704
Waist circ. (cm) [b]	97.5 (12.1)	96.9 (11.7)	100.0 (13.8)	0.109
Hip circ. (cm) [b]	99.9 (8.29)	99.5 (7.72)	101.7 (10.28)	0.100
Waist hip ratio (WHR) [b]	0.97 (0.07)	0.97 (0.07)	0.98 (0.08)	0.382
WHR >1	87 (34.4)	69 (33.7)	18 (37.5)	0.614

[a] p-value based on Chi-squared test unless stated otherwise
[b] Mean (sd), p-value based on two-way t-test

Table 5.6 shows the body composition parameters in those who underwent DXA scanning (n=108). There was no difference in fat free mass, fat mass, fat mass ratio, lean limb mass (ASM) or skeletal mass index (ASM/height^2) between frail and non-frail individuals. Around 50% of those with and without frailty were classified as having low muscle mass based on gender-specific cut-offs on the skeletal mass index. Presarcopenia was more common in those without frailty (40.3% versus 6.5%, p<0.001) and conversely sarcopenia more common in those with frailty (45.2% versus 10.4%, p<0.001). It should be noted that eight individuals met the criteria for sarcopenia but not frailty suggesting that sarcopenia can exist in the absence of frailty. There were no differences in levels of sarcopenic obesity or DXA diagnosed lipodystrophy between the two frailty groups.

Table 5.6: DXA based body composition parameters by frailty status

	Full cohort N=108 (%)	Not frail N=77 (%)	Frail N=31 (%)	p-value [a]
Fat free mass (kg) [b]	50.9 (8.37)	51.3 (8.06)	49.9 (9.14)	0.445
Fat mass (kg) [c]	23.5 (16.2-30.1)	23.3 (16.2-28.5)	23.7 (16.3-36.3)	0.279
Fat mass ratio [b]	1.50 (0.55)	1.53 (0.53)	1.42 (0.58)	0.335
ASM (kg) [b]	22.3 (4.37)	22.5 (4.26)	21.8 (4.64)	0.417
SMI [b]	7.32 (1.18)	7.33 (1.12)	7.32 (1.31)	0.953
Low muscle mass	55 (50.9)	39 (50.6)	16 (51.6)	0.928
Normal muscle mass	53 (49.0)	38 (49.4)	15 (48.4)	**<0.001**
Presarcopenia	33 (30.6)	31 (40.2)	2 (6.5)	
Sarcopenia	16 (14.8)	7 (9.1)	9 (29.0)	
Severe sarcopenia	6 (5.6)	1 (1.3)	5 (16.1)	
Presarcopenia	33 (30.6)	31 (40.2)	2 (6.5)	**<0.001**
Sarcopenia	22 (20.4)	8 (10.4)	14 (45.2)	**<0.001**
Sarcopenic obesity	7 (31.8)	2 (25.0)	5 (31.8)	0.604
Lipodystrophy	20 (18.5)	16 (20.8)	4 (12.9)	0.340

[a] p-value based on Chi-squared test unless stated otherwise
[b] Mean (sd), p-value based on two-way t-test
[c] Median (IQR), p-value generated with MWU-test
ASM= appendicular skeletal mass (lean limb mass)
SMI= skeletal mass index (ASM/height^2)

Body composition was also assessed using limb circumference and skinfold measurements, which have been associated with sarcopenia and frailty. Table 5.7 summarises these measures across the full cohort and by frailty status. There was no difference in mid-calf or mid-arm muscle circumference based on frailty. A higher proportion of frail individuals had a low muscle mass based on calf circumference less than 31cm and MAMC in the lowest tertile but neither reached statistical significance. Once again, fat free mass, fat mass and proportions with low muscle mass did not vary between frailty groups. Approximately one third of participants were classified as having low muscle mass using this method (36.8% if frail versus 32.1% if non-frail, p=0.326). Sarcopenia was significantly more common in those with frailty seen in 36.8% (versus 3.3%, p<0.001). No frail

individuals were presarcopenic but six non-frail participants demonstrated sarcopenia in the absence of frailty.

Table 5.7: Anthropometry based body composition parameters by frailty status

	Full cohort N (%)	Not frail N (%)	Frail N (%)	p-value [a]
Calf circumference (n=250)				
Mid-calf circ. (cm) [b]	37.7 (3.95)	37.8 (3.99)	37.3 (3.76)	0.365
Low calf circ. (<31cm)	8 (3.2)	5 (2.5)	3 (6.5)	0.156
Mid-arm muscle circumference (n=247)				
MAMC (cm) [b]	25.8 (3.60)	25.8 (3.68)	25.5 (3.28)	0.593
Lowest tertile MAMC	83 (33.6)	65 (32.3)	18 (39.1)	0.379
Calculated body composition (n=222)				
Fat free mass (kg) [b]	55.5 (8.58)	55.9 (8.50)	54.3 (8.99)	0.311
Fat mass (kg) [b]	24.9 (8.03)	24.9 (7.26)	25.3 (11.2)	0.772
Low muscle mass	73 (32.9)	59 (32.1)	14 (36.8)	0.326
Sarcopenia	20 (9.0)	6 (3.3)	14 (36.8)	**<0.001**
Sarcopenia groups				
Normal	149 (67.1)	125 (67.9)	24 (63.2)	**<0.001**
Presarcopenia	53 (23.9)	53 (28.8)	0 (0.0)	
Sarcopenia	15 (6.8)	6 (3.3)	9 (23.7)	
Severe sarcopenia	5 (2.3)	0 (0.0)	5 (13.2)	

[a] p-value based on Chi-squared test unless stated otherwise
[b] Mean (sd), p-value based on two-way t-test

To examine whether sarcopenia or other body composition parameters predicted frailty we undertook univariate and multivariable logistic regression. Of the 48 participants identified as frail, 31 (64.6%) were included in the DXA subgroup and 38 (79.2%) in the calculated sarcopenia group. Table 5.8 summarises the results of these analyses, demonstrating crude associations were mainly strengthened after adjusting for age and BMI. Low compared to normal muscle mass was not associated with frailty when measured by DXA or anthropometry. Sarcopenia was statistically significantly associated with frailty increasing the odds between 7-17 times depending on the method of assessment used. For both DXA and anthropometry there was evidence of a linear trend of frailty risk for increasing sarcopenic category (normal, pre-, sarcopenic, severe sarcopenia), using normal

muscle mass as the reference group. For both methods, an increase in sarcopenia level was associated with around a 3-fold increase in the adjusted odds of frailty (DXA aOR 3.42; 95%CI 1.79-6.56 & Anthropometry aOR 3.05; 95%CI 1.81-5.13, both p<0.001). The presence of sarcopenia with obesity (sarcopenic obesity) was associated with an 8-fold increased risk of frailty (p=0.017), but lipodystrophy was not. Being in the lowest tertile for mid-arm muscle circumference increased the odds of frailty by 3.6 times (aOR 3.58; 95%CI 1.28-10, p=0.015) and there was a suggestion that increasing mid-calf circumference was associated with lower frailty (aOR 0.88, p=0.06), corroborated by an increased odds of frailty seen for those in the lowest tertile (aOR 4.71, p=0.06), though neither achieved statistical significance.

Table 5.8: Uni- and multivariable analysis of the association between frailty and body composition

	Association with frailty			
	Crude OR (95% CI)	**aOR [a]**	**95% CI**	**p-value**
DXA based values				
Low muscle mass	1.04 (0.45-2.39)	2.11	0.67-6.59	0.201
Sarcopenia	7.10 (2.57-19.7)	16.53	4.64-58.9	**<0.001**
Increasing sarcopenia (trend)	1.83 (1.15-2.91)	3.42	1.79-6.56	**<0.001**
Sarcopenic obesity	7.21 (1.31-39.5)	8.15	1.45-45.8	**0.017**
Lipodystrophy	0.56 (0.17-1.84)	0.60	0.94-1.06	0.991
Anthropometry based values				
Low muscle mass	1.24 (0.60-2.56)	1.54	0.65-3.62	0.325
Sarcopenia	17.31 (6.07-49.3)	26.31	8.13-85.2	**<0.001**
Increasing sarcopenia (trend)	2.27 (1.48-3.50)	3.05	1.81-5.13	**<0.001**
Mid-calf circ. (cm)	0.96 (0.88-1.04)	0.88	0.79-1.01	0.060
Low calf circ.	2.78 (0.64-12.1)	4.71	0.94-23.6	0.059
Low MAMC [b]	1.35 (0.69-2.61)	3.58	1.28-10.0	**0.015**

[a] Adjusted for age and BMI
[b] Lowest compared to highest tertile (ref)

5.1.4 Discussion

Using DXA based parameters low muscle mass was common in this cohort affecting over 50%. A lesser proportion met the criteria for sarcopenia at 20.4%, which was lower when anthropometric measurements were used at 9%. Sarcopenia prevalence was higher in those with frailty at 36.8-45.1% and when defined by either technique was associated with frailty.

Based on EWGSOP criteria, of the all those who undertook a DXA scan less than half had a normal muscle mass, with 20.4% classified as sarcopenic or severely sarcopenic and a further 30.6% having low muscle mass alone making them presarcopenic. This is higher than has been seen in research conducted in those with HIV. Using the same criteria, Wasserman and colleagues' cross-sectional study of cART experienced PLWH aged over 45 (mean 53) recruited from clinics in New York, USA showed a prevalence of sarcopenia of 5% and 20% for presarcopenia [329]. Our results are more aligned to those of a small Brazilian study where in a group of 33 HIV-positive individuals on cART aged over 50 (mean age 57) the prevalence of sarcopenia and presarcopenia was 24.2% and 12.1% respectively. This was significantly higher than the HIV-negative control group where 6.7% were sarcopenic despite the group being older (mean age 70), supporting an excess of sarcopenia in those with HIV [330]. Where sarcopenia was assessed using a muscle mass cut-off alone, a study of 64 HIV-positive men with mean age of 41.5 showed low muscle mass in 21.9% of participants [332]. Similar figures were seen in a further Brazilian study with low muscle mass seen in 27.8% of men and 20.7% of women with HIV and no lipodystrophy, which increased in those with lipodystrophy to 44.8% and 41.7%; but was even higher in their HIV-negative control group at 63.3% and 45.4% of men and women respectively. The high rates of low muscle mass in the control group was thought to reflect older age and recruitment from hospital services and therefore may not be reflective of the general population [334]. We too examined lipodystrophy based on DXA diagnosis, observing no differences in or associations with sarcopenia or frailty status.

To put this in the context of HIV-negative cohorts, a systematic review of sarcopenia prevalence based EWGSOP criteria ranged between 1-29%

depending on population studied [335]. More specifically, Cooper et al. performed one-off screening for sarcopenia using these criteria on 1566 participants from the longitudinal British Birth Cohort at ages 60-64. Here they showed a low muscle mass in 20.8% of men and 30.7% of women, and sarcopenia prevalence of 4.6 and 7.3% respectively [336]. Further British cohorts found sarcopenia to be present in 6.8% of those in the Hertfordshire Sarcopenia Study (mean age 73) and 4.6% of men and 7.9% of women enrolled to the Hertfordshire Cohort Study (mean age 67) [320]. Lastly, a population study investigating sarcopenia (DXA plus grip strength) in 1421 HIV-negative French individuals aged over 45, found sarcopenia in 15.5% [337].

In this study sarcopenia based on DXA diagnosis was associated with older age, lower BMI and body mass, and in terms of HIV factors, there were significant associations with older age at diagnosis, lower nadir CD4 and current CD4 <350 (p=0.05) and non-significant trends towards diagnosis of the age of 50 and shorter HIV duration. These mirror findings in studies of sarcopenia in those with [329] and without HIV [335,337], particularly low BMI [331,332]. These predictors might suggest the compounding effects of natural ageing, combined with more advanced immunosuppression and potential associated inflammation at diagnosis may contribute to an acceleration of muscular ageing.

We showed a lower prevalence when sarcopenia was assessed using anthropometric measures where low muscle mass was present in 32.9% of participants, representing 23.9% presarcopenia and 9% sarcopenia respectively. This did include a larger proportion of the cohort as we were limited in the number of DXA scans we could perform, and although we saw good correlation between DXA and anthropometry derived mass values, it does have inherent measuring biases in that it is more subjective than DXA, though the same researcher conducted all measurements to the same protocol to minimise this. Additionally, studies have demonstrated differing sarcopenia prevalence within the same cohort dependent on criteria chosen [338].

Sarcopenia was related to frailty status in this cohort, with sarcopenia increasing with worsening frailty state. Sarcopenia was seen in 18.2% of those with prefrailty, increasing to 45.1% in frail individuals, with a reverse trend seen for

presarcopenia, which becomes less prevalent as frailty state increases. Sarcopenia and increasing sarcopenic states were significantly associated with increased odds of frailty. The relationship with frailty and sarcopenia in those with HIV has not been explicitly examined in the literature, with the closest assessment from a small US study (n=72, mean age 52) by Erlandson et al. who defined sarcopenia by low muscle mass alone showing that of those with low function (frail by Fried phenotype or low performance on the Short Physical Performance Battery) 50% were sarcopenic, compared to 35% overall. Additionally, appendicular skeletal mass index, lean body mass and appendicular lean mass were all significantly lower in those considered low function [331].

Our findings support that sarcopenia is occurring at higher prevalence in those with HIV and at earlier ages than seen in the HIV-negative population and may represent another manifestation of premature ageing in PLWH. The fact that the prevalence is higher in this study may be for a number of reasons, firstly the cohort is older, aged over 50 at which point muscle mass starts to decline sharply [339]. Additionally, other HIV studies have not examined sarcopenia in the context of frailty, with a third of those included in this study classified as frail and 40% prefrail, in whom it might be anticipated that prevalence would be higher, particularly in the presence of shared diagnostic characteristics.

There is potential for overlap between sarcopenia and frailty particularly when examined in the context of Fried's phenotypic criteria [315,319,340], where sarcopenia could contribute to all five, especially given the discussed effects on weight, grip strength and mobility. Decline in muscle function may also limit physical activity and energy balance resulting in exhaustion. This overlap is confirmed in this study as we demonstrated that all frailty criteria were significantly higher in those with sarcopenia. Cesari et al. examined the relationship with muscle parameters rather than sarcopenia specifically showing that in a group of older adults, with mean age 74.8 years and frailty prevalence 8.8%, frailty was associated with significantly lower muscle area and density, and higher fat area [341]. However, Reijnierse et al. present data from a cross-sectional study of community dwelling older adults (mean age 82.4), where concordance with frailty and sarcopenia was low, with sarcopenic individuals more likely to be frail than frail individuals to have

sarcopenia suggesting that they represent different entities. Interestingly those with sarcopenia were more likely to be deemed frail using the phenotype model rather than on Rockwood's brief clinical frailty tool, supporting the notion that the phenotype may rely more heavily on muscle loss [342].

Certainly, low muscle mass was prevalent in this cohort affecting approximately 50% of all receiving a DXA scan and the same proportion in each of the three frailty categories. In our approach, sarcopenia and frailty certainly overlap as there are shared diagnostic criteria, however they are not mutually exclusive as shown from our results. 8 (18.2%) of prefrail individuals were sarcopenic and over half (54.9%) of those defined as frail were not sarcopenic. Frailty appeared to be less related to low muscle mass alone or by differences in other individual body composition parameters such as fat free mass, fat mass, body weight, and BMI, which showed no difference between frail and non-frail individuals however measured. Additionally, low muscle mass alone did not predict frailty, only sarcopenia itself or increasing severity of sarcopenia and sarcopenic obesity were associated with increased odds of frailty. This suggests that there is more to frailty than sarcopenia and muscle pathology, supporting its status as a multisystem disorder.

Apart from sarcopenia we showed no difference in any other body composition parameter between those with and without frailty. However, in the literature aspects of body composition have been associated with frailty in those with HIV. Kooij et al. in AGEhIV showed higher frailty states (prefrail/frail versus robust) to be associated with higher waist-to-hip ratio and current BMI <20kg/m^2 [190]. Low BMI predicted frailty in South Africans with HIV[181] and a low BMI (<18kg/m^2) was also significantly more prevalent among frail persons (9% vs. 2%; p<0.03) in the study by Onen et al. [180]. Conversely in a study where frailty was based on a composite score rather than a known frailty screening tool, frailty was associated with higher BMI, waist circumference, fat mass and trunk fat [195]. There were very few individuals classified as underweight in this cohort with the majority of participants classified as overweight or obese, which may explain the lack of association seen here.

The examination of sarcopenia and frailty in the context of HIV is lacking in the literature and represents a strength of this study. In addition, the use of a recommended diagnostic tool for the assessment of body composition in the form of DXA using a recognised algorithm that encompasses both muscle mass and markers of muscle function. This dual approach has been lacking in many other studies which have relied on muscle mass alone, with criticism that muscle function may be more important than muscle mass alone as it is better correlated with functional decline [343,344].

There are however some limitations to these investigations. Only two thirds of those with frailty consented to attend for a DXA scan, which probably underrepresented those with higher frailty states or functional disorders as travel to Brighton was required, as such we may have underestimated sarcopenia in those with frailty. Though we achieved a good match between those with and without frailty that underwent DXA scanning there was significantly less non-white ethnicity represented which again may reflect that the main recruitment of non-white participants was outside of Brighton. Therefore, these findings may not be generalisable to an ethnically diverse HIV population or indeed to women as no cases of sarcopenia were seen. Also, though we chose a recognised algorithm, there is no validated tool in PLWH and the definition of low muscle mass is based on young person population norms, which may not be representative of the HIV-positive population. Once again, these data are cross-sectional in nature and therefore any relationships cannot be said to be causal.

5.1.5 Conclusion:

We demonstrate that around a half of those studied had low muscle mass, with sarcopenia being more common than demonstrated in the HIV-negative and HIV-positive literature to date. Sarcopenia is more prevalent in those with frailty, and increases the odds of a frail state. No other body composition changes were associated with frailty. Longitudinal evaluations of frailty alongside muscle mass and muscle function in those with HIV may help in defining whether and if so how the natural ageing of the musculature varies in PLWH to highlight potential targets for intervention.

5.2 Nutrition

5.2.1 Introduction

Older age may be associated with alterations in nutritional intake, with tendency towards reduction with age [345]. Inadequate nutritional status is thought to be associated with frailty, with complex interlinking mechanism likely to be at play. However, poor nutrition may promote unintentional weight loss, including decline in muscle mass if protein deficient. Both may in turn impede muscle functional ability leading to exhaustion and lower physical ability [346].

Diet quality, particularly sufficient daily energy intake rather than individual nutrients, has been associated with frailty in older men (>65) [347]. Others have investigated the role of protein in preventing loss of muscle mass by ameliorating muscle catabolism [348], with less frailty (incident and prevalent) observed in older individuals with higher protein consumption [349–351]. A dietary protein intake of around 0.8g/kg body weight/day is generally recommended, however an international expert working group suggest that this may be insufficient in older adults (≥65), who may experience inadequate protein intake and a reduced ability to utilise available protein, despite a greater need [352]. A higher intake at 1.0-1.2g/kg/day, increasing to >1.2g/kg/day for those with acute or chronic disease, including frailty has been advocated in conjunction with physical activity where possible[352].

The InChianti Study examined frailty and nutritional status by means of a food frequency questionnaire in 1017 adults over 65 in which they demonstrated that energy intake ≤21kcal/kg/day, low protein and low levels of vitamins D, E and C predicted frailty. A low nutritional score, formed of deficiencies in at least three nutrients was associated with a doubling of the risk of frailty compared to those with adequate nutrition (OR 2.12; 1.29-3.50) [353]. The large NHANES III trial of 4731 American older adults (>60) showed high prevalence of frailty at 21.7%, which was associated with lower overall energy intake but similar macronutrient intake than those without frailty[189]. Additionally, a more ‘liberal diet’ with participants consuming >10% more than their daily energy requirements, was associated with a significantly lower incidence of frailty after eight years, without an increase in obesity or cardiovascular and metabolic disease [354].

The role of more global dietary patterns was examined in a further sub-study using the InChianti cohort which showed lower incident frailty (OR 0.30; 95% CI 0.16-0.66) and lower risk of reduced physical activity in those with high adherence to the Mediterranean diet [355–357]. These all lend support to overall diet quality over particular macro- or micronutrients. Additionally, direct aetiological links between specific nutritional deficiencies and frailty and/or sarcopenia are yet to be proven with nutritional intervention studies in frailty broadly failing to show benefit. Therefore currently, maintaining an adequate diet in line with regular healthy lifestyle measures is recommended [358].

Nutrition is important in PLWH, particularly for those with symptomatic infection or early in treatment where changes in weight and body composition may occur as described, with fat redistribution and loss of lean mass. Additionally, alterations in lipid and glucose metabolism resulting from cART may benefit from dietary modification. Lastly, immune parameters and inflammation may be influenced by the nutritional status of the individual. As such, taking a dietary history, assessing for nutritional deficiencies and providing nutritional advice in PLWH has been recommended [359,360], and is supported by a position statement from the American Dietetic Association [361]. However, existing methods of nutritional screening may not be adequate in older adults with HIV [360].

A Cochrane review of interventional studies of macronutrient supplementation in PLWH in high and low-income settings demonstrated that targeted dietary supplementation with balanced macronutrients can increase energy and protein intake. However, the studies were heterogeneous and often of low quality meaning that any effect on mortality, morbidity, weight, and immune parameters remain unclear [362]. Inconsistent results were also seen in a Cochrane review of micronutrient studies in HIV, where vitamin A, D and zinc showed no effect, selenium may have the potential to increase CD4 counts and that multi-nutrient supplements may deliver positive effects to pregnant women with HIV, but all warrant further investigation [363]. In terms of practical recommendations, an international expert working group reviewed the available data and suggested for adults with asymptomatic HIV that daily energy intake should be 110% of that recommended for HIV-negative individuals, with no change to current suggested

intakes for macro- and micronutrients other than to achieve the increased energy demands [364]. They make a number of suggestions for research and policy priorities around nutrition and HIV, acknowledging that the importance of nutrition in HIV and ageing represents a major gap in the knowledge, encouraging the inclusion of older adults in interventional nutritional studies [364].

An additional issue raised in explorations of diet and nutrition is the idea of food insecurity, which describes an inability to access sufficient food to meet one's dietary needs, which may be due to physical, social, or economic reasons. It has been associated with frailty in individuals with [189] and without HIV[365]. A small study of 50 individuals aged over 45 with HIV, showed a frailty prevalence of 16%, with frail individuals significantly more likely to report food insecurity than those without (63% versus 10%, p=0.02) [189]. Furthermore, in PLWH food insecurity is associated with adverse HIV outcomes [366] and mortality [367].

Section aims:

We aim to describe the nutritional intake for the cohort based on food frequency data, examining the effect of nutrition on frailty. We hypothesise that frail individuals will exhibit a poorer nutritional state than those without frailty.

5.2.2 Methods

All participants were asked to complete the EPIC-Norfolk food frequency questionnaire (FFQ). Individuals completed the tick-box matrix stating how often, on average, they consume 130 food and drink items, rating intake from never or less than once a month up to greater than 6 times per day for each. Additional information was collected on milk, cereal, fats, meat, fruit and vegetable intake. Responses were converted to estimated daily intake values for a number of macro- and micronutrients using open access FETA software [209].

Core macro- and micro-nutrients were analysed as continuous variables, presenting appropriate average and associated variance measures. Intake per kilogram body weight was calculated for total energy and protein intakes to compare to published literature on optimal intakes. The UK government recommended dietary reference values were used to dichotomise participants' intake as deficient or adequate for each nutrient of interest. Table 5.9 shows the

UK dietary reference values, which were set by the Committee on Medical Aspects of Food and Nutrition Policy (COMA) in 1991 [368]. COMA has been subsequently replaced by the Scientific Advisory Committee on Nutrition (SACN). Recommendations are either based upon the estimated average requirement (EAR), or the reference nutrient intake (RNI), which is the amount of a nutrient sufficient to meet the needs of nearly everyone (97.5%).

Table 5.9: UK recommended daily nutrient intakes for men and women.

	Males		Females	
	Age	**Recommended daily intake**	**Age**	**Recommended daily intake**
Energy	45-54	2581	45-54	2103
(Kcal/day)	55-64	2581	55-64	2079
EAR [a]	65-74	2342	65-74	1912
	75+	2294	75+	1840
Protein (g/kg)	50+	0.75	50+	0.75
Micronutrients [b]				
Vitamin A (µg)	50+	700	50+	600
Thiamine (mg)	50+	0.9	50+	0.8
Riboflavin (mg)	50+	1.3	50+	1.1
Niacin (mg)	50+	16	50+	12
Vitamin B6 (mg)	50+	1.4	50+	1.2
Vitamin B12 (µg)	50+	1.5	50+	1.5
Vitamin C (mg)	50+	40	50+	40
Folate (mg)	50+	200	50+	200
Iron (mg)	50+	8.7	50+	8.7
Calcium (mg)	50+	700	50+	700
Zinc (mg)	50+	9.5	50+	.0
Selenium (µg)	50+	75	50+	60

[a] EAR= estimated average requirement, [b] Based on reference nutrient intake (RNI)

5.2.3 Results

250 participants completed the FFQ, with all 205 non-frail and individuals and 45/48 (93.8%) of frail individuals contributing to nutritional data analysis. Table 5.10 shows the estimated daily intake for the examined macro- and micronutrients for the whole group and then by frailty status. There were no significant differences in either energy or major macronutrient intake. Looking at the measured micronutrients, there was a slightly lower intake of vitamins B12 and C in those with frailty but these failed to reach statistical significance. The

only significant difference was seen with median vitamin D intake (ergocalciferol), which was lower in frail individuals. Data on alcohol intake was collected in the FFQ, demonstrating that those with frailty report a significantly lower alcohol intake than those without (p=0.024). This corroborates the findings from verbally reported alcohol intake gained by direct questioning during the medical interview, as described in chapter 4.

Univariate and multivariable logistic regression (as described previously) failed to demonstrate an association between any of the listed nutrients and frailty in this cohort, including for both vitamin D and alcohol intake. Additionally, each nutrient was examined by quintile, and was assessed for the presence of linear trend and dose-relationship in relation to frailty risk by change in quintile. This was only seen for alcohol intake, where a 34% reduction in odds of frailty were observed per quintile increase in consumption (OR 0.66; 95% CI 0.48-0.90, p=0.009). Where no trend was observed, those with in the lowest intake quintile were compared to those in the highest for each respective nutrient. Those in the lowest quintile for vitamin D had a 4.5-fold increased risk of frailty compared to the highest group (OR 4.47; 95% CI 1.36-14.76, p=0.014), though higher intakes of Vitamin D showed no association. No other nutrient predicted frailty risk.

Where dietary recommendations exist, nutritional deficiencies were examined in relation to frailty group as shown in Table 5.11. Though not statistically significant, where daily requirements were set lower for both energy (21Kcal/kg/day) and protein intake (0.75g/kg/day), those failing to achieve these targets were more often frail. At higher suggested intake for energy (25Kcal/kg/day) around half of participants in each group were failing to meet this target, which was similar for the higher protein intake (1.2g/kg/day) at 59.5% and 68.9% for non-frail and frail participants respectively. Frail individuals were significantly more likely to fail to meet the recommended daily intake of vitamin C compared to those without frailty (6.7 versus 1.5%, p=0.039), though absolute numbers are small (n=3 in each group). Deficiency in no other nutrient was significantly associated with frailty, though the proportion of individuals failing to meet recommended intakes of protein, thiamine, riboflavin and zinc was higher in those with frailty.

Lastly, we examined the effect of having any one nutritional deficiency from the 14 with RDA levels. Participants had median deficiency in two of the listed nutrients (IQR 0-4) with no difference seen between frail and non-frail individuals (p=0.203). The presence of any nutritional deficiency was not-significantly associated with frailty in univariate or multivariable analysis (p=0.142 and 0.669 respectively). To assess the effect of global dietary influence, the effect of 3 more nutritional deficiencies was assessed. Frail individuals were statistically more likely to demonstrate multiple deficiencies (48.9% versus 33.2%, p=0.047), and in univariate analysis the presence of three or more nutritional deficiencies was associated with a 93% increase in the odds of frailty (OR 1.93; 95% CI 1.00-3.70, p=0.049), though this effect was not seen after adjusting for age, gender, HADS score and number of comorbidities (p=0.449).

Table 5.10: Relationship between frailty status and nutritional intake

	Full cohort (n=250)	Non-frail (n=205)	Frail (n=45)	p-value [a]
Energy (Kcal) [a]	2032.2 (664.4)	2038.3 (631.5)	2004.4 (823.5)	0.759
Macronutrients				
Protein (g) [a]	90.5 (28.6)	91.3 (28.6)	87.0 (28.7)	0.367
Protein (g/kg) [a]	1.2 (0.43)	1.2 (0.43)	1.1 (0.46)	0.483
Carbohydrate (g) [b]	220.0 (179.4-270.8)	222.1 (180.5-270.7)	211.3 (169.2-271.6)	0.633
Total fat (g) [b]	74.9 (60.8-95.3)	73.9 (62.2-95.3)	76.4 (48.7-94.1)	0.493
Micronutrients				
Vitamin A (µg) [b]	1350.0 (874.6-1816.7)	1354.8 (874.6-1815.5)	1301.4 (910.7-1816.7)	0.780
Thiamine (mg) [a]	1.63 (0.56)	1.64 (0.56)	1.60 (0.55)	0.630
Riboflavin (mg) [a]	2.23 (0.84)	2.21 (0.84)	2.32 (0.85)	0.403
Niacin (mg) [a]	24.9 (8.4)	25.1 (8.5)	24.0 (8.2)	0.432
Vitamin B6 (mg) [a]	2.4 (0.76)	2.4 (0.75)	2.4 (0.78)	0.626
Vitamin B12 (µg) [b]	8.1 (5.6-11.0)	8.3 (5.6-11.1)	7.5 (5.6-9.6)	0.424
Vitamin C (mg) [b]	117.3 (85.6-164.8)	119.4 (87.1-163.7)	101.8 (75.6-169.5)	0.344
Vitamin D (µg) [b]	3.1 (2.3-5.1)	3.2 (2.4-5.1)	2.7 (1.9-4.1)	**0.033**
Vitamin E (mg) [b]	11.6 (9.2-14.6)	11.6 (9.3-14.5)	11.4 (8.0-15.5)	0.613
Folate (mg) [a]	322.1 (116.2)	322.4 (118.4)	320.9 (107.0)	0.941
Zinc (mg)	10.1 (3.3)	10.2 (3.3)	9.7 (3.2)	0.380
Selenium (µg)	71.6 (27.1)	72.5 (26.2)	67.7 (31.0)	0.285
Iron (mg) [a]	12.2 (4.2)	12.3 (4.2)	11.6 (4.1)	0.263
Calcium (mg) [a]	980.1 (340.3)	979.0 (338.6)	985.0 (52.5)	0.915
Other				
Alcohol (g) [b]	4.0 (0.76-11.5)	4.87 (0.76-12.5)	1.52 (0.0-6.4)	**0.024**

[a] Mean (sd), p-value based on two-way t-test unless stated otherwise
[b] Median (IQR), p-value generated with MWU-test

Table 5.11: Relationship between nutritional deficiency and frailty status

	Recommended daily intake	Failure to meet daily intake		p-value [a]
		Non-frail (n=205)	Frail (n=45)	
Energy (Kcal/kg)	>21	60 (29.3)	19 (42.2)	0.091
	>25	109 (53.2)	24 (53.3)	0.984
	UK EAR [b]	42 (20.5)	12 (26.7)	0.362
Macronutrients				
Protein (g/kg) [c]	>0.75	25 (12.2)	10 (22.2)	0.079
Protein (g/kg)	>1.2	122 (59.5)	31 (68.9)	0.242
Micronutrients [d]				
Vitamin A (µg)	Males >700 Females >600	31 (15.1)	7 (15.6)	0.942
Thiamine (mg)	Males >0.9 Females >0.8	11 (5.4)	3 (6.7)	0.731
Riboflavin (mg)	Males >1.3 Females >1.1	17 (8.3)	5 (11.1)	0.546
Niacin (mg)	Males >16 Females >12	25 (12.2)	7 (15.6)	0.541
Vitamin B6 (mg)	Males >1.4 Females >1.2	2.38 (0.75)	2.32 (0.78)	0.626
Vitamin B12 (µg)	>1.5	0	0	-
Vitamin C (mg)	>40	3 (1.46)	3 (6.67)	**0.039**
Folate (mg)	>200	26 (12.7)	4 (8.9)	0.478
Zinc (mg)	Males >9.5 Females >7.0	86 (42.0)	24 (53.3)	0.164
Selenium (µg)	Males >75 Females >60	116 (56.6)	31 (68.9)	0.129
Iron (mg)	>8.7	35 (17.1)	9 (20.0)	0.641
Calcium (mg)	>700	33 (16.1)	8 (17.8)	0.783

[a] p-value based on Chi-squared test unless stated otherwise
[b] UK EAR for energy: Males aged 50-64- 2581, 65-74- 2342 & >75- 2294. Women aged 50-54- 2103, 55-64- 2079, 65-74- 1912 & >75- 1840Kcal/day
[c] UK recommended daily intake for adults.
[d] Based on reference nutrient intake

5.2.4 Discussion

Using nutritional data derived from the EPIC-FFQ we showed no difference in the calculated intake of macro- and most micronutrients between those with and without frailty, except for vitamin D and alcohol. Lower vitamin D intake was associated with significantly higher odds of frailty, with higher alcohol intake appearing to reduce the likelihood of frailty.

Vitamin D intake was significantly lower in those with frailty. Individuals with the lowest quintile of vitamin D intake had 4.5-times the odds of frailty compared to those with the highest quintile only. Vitamin D deficiency is common in those with and without HIV, with the WIHS assessing vitamin D levels in 1778 women showing deficiency in 63% of participants [369]. Similar levels were seen in a French HIV-positive cohort with male predominance where 87% had low vitamin D and 31% were deficient [370]. Low vitamin D has been associated with frailty [353,371,372], with a potential mechanism conferred through the effect of vitamin D deficiency on the development of sarcopenia [373]. As such vitamin D supplementation has been explored as a potential intervention in those with frailty and sarcopenia, with a RCT of 380 sarcopenic participants comparing vitamin D and leucine-rich whey protein supplementation to calorie equivalent placebo showing improvements in muscle mass and lower extremity function after three months [374]. Vitamin D has been of interest for some time within HIV due to its potential role in bone mineral loss and on wider organ systems [375]. Erlandson et al. present the only study examining vitamin D in the context of frailty in HIV showing no association between low measured vitamin D and functional status [331]. In the context of this study, we must be cautious about any potential association. The FFQ provides data on nutritional intake only, it does not consider any vitamin D supplementation that the individual may be on, time of year enrolled to the study or indeed the role of sunlight exposure. As such, though intake may be lower in those with frailty, circulating vitamin D levels may be normal, which were not measured in this study. Such a situation was seen in a Dutch study of sarcopenia associations in community-dwelling older cohort, where vitamin D intake was low but serum level normal [376].

Alcohol intake was significantly higher in non-frail individuals and appeared to be a negatively associated with frailty, which mirrors findings gained from direct questioning around behavioural risk factors as discussed in chapter 4. Alcohol has been demonstrated to be a protective factor for frailty in population studies. In the Lausanne 65+ cohort of 1564 French adults aged 65-70, when compared to light to moderate alcohol intake, those taking no alcohol had twice the odds of both prevalent and incident vulnerability (prefrail/frail state) at 3 years, with no association seen for higher alcohol intakes [377]. Similar findings have been shown in cohorts from Spain with respect to protective effect of drinking with meals and as part of the Mediterranean diet [378] and in Eastern European adults aged 45-69 [379]. However, these findings are not universal with others reporting no association [123].

The relationship between alcohol and frailty is likely to be complex and we cannot comment on causality or the direction of any relationship. It is possible that those with frailty may avoid alcohol due to more complex medical problems and drug regimens. This is supported by Hu et al. in their evaluation of the association of alcohol consumption and physical limitations in middle-aged adults in Eastern Europe where though lifelong abstinence was still associated with limitation, the highest risk was in those who stopped or reduced drinking due to health problems, thus moving less healthy heavier drinkers into lower drinking groups [379]. Additionally, those with frailty may be less able to access and consume alcohol compared to non-frail individuals. An explanation of how light-moderate alcohol intake may protect against frailty, may be due to anti-inflammatory properties. A study by Shah demonstrated that CRP and alcohol levels followed the same J-shaped curve, with low-moderate alcohol being associated with lower CRP levels and lower incident frailty [380]. Though the relationship warrants further evaluation alcohol is associated with a range of different organ system pathologies that may offset any potential benefit gained in terms of frailty. Indeed in those with HIV compared to those without, a large study using VACS data suggested no protective effect in terms of mortality or physiological injury (VACSI score) at any level of alcohol consumption, with higher risk or adverse outcomes seen at lower levels of consumption in PLWH [381].

As discussed higher levels of protein and energy intake may have a role in protecting against frailty. We saw higher rates of failure to meet recommended daily protein intake when set at lower and higher levels, and energy intake using the UK EAR and the 21kcal/kg/day used in the InChianti study in those with frailty compared to those without, yet these failed to reach statistical significance. Frail individuals were significantly more likely to fail to meet the recommended vitamin C intake, which predicted frailty in the InChianti study, potentially through absence of its antioxidant properties that are essential in optimal cellular functioning. However, in this study only six participants were classified as deficient, therefore this would warrant re-evaluation in a larger cohort study.

There is a suggestion that global nutritional state is important in terms of frailty, with cumulative deficiencies conferring higher frailty risk [353]. However, we showed that the median number of deficiencies did not vary by frailty status, and increasing number of deficiencies did not confer an enhanced risk of frailty in this cohort. These findings may be explained by the relative heterogeneity of our group, with the majority being of white ethnicity, mostly male and all living in a geographically restricted area, which may have reduced dietary diversity. Though we had an excellent rate of completion of the FFQ at 98.8%, all three non-completers were frail, which if they followed the trend of lower nutritional intakes may possibly have revealed stronger associations between nutritional impairment and frailty.

There are some limitations this investigation of nutrition and frailty. We utilised a food frequency questionnaire, which is based on dietary recall over the previous year. This opens it up to recall bias, and potential to over or under report food types that are more or less socially desirable respectively. Additionally, the questionnaire may not be representative of true diet of all participants as firstly it assumes a standard portion size, which may of course be smaller or greater for some individuals; secondly it is skewed toward a westernised diet which may not be observed by all of the participants included in this study; thirdly it is based around raw ingredients, which may not reflect what is actually consumed, such as the use of pre-prepared foods that could be scrutinised if an alternative method such as a food-diary was used. The FFQ also calculates an estimated nutritional

intake based on responses rather than actual measured values or biomarker correlates as discussed with vitamin D level. Additionally, deficiency and recommended intakes are based on UK National data and average requirement, which may not be applicable to PLWH. They may have different needs due to factors such as gastrointestinal upset, malabsorption or adverse effects of medications. The FFQ has also been criticised in terms of its reliability in relation to other nutritional tools [233,382]. FFQs have been employed in studies of PLWH with Hendricks et al. showing the FFQ (block FFQ) to underestimate dietary intake of energy, protein and a number of micronutrients with poor correlation seen with a 3-day food diary, which was more marked in men [234].

We are unable to comment on specific diets, such as the Mediterranean diet, which may be beneficial in frailty avoidance [355]. We also have no data on food security, which appears to be a particular issue for PLWH [383], being associated with adverse outcomes [367] including the presence of frailty [189]. Food insecurity is linked to adverse socioeconomic conditions, which were more prevalent amongst our frail participants therefore it is an issue that should be investigated further.

5.2.5 Conclusion

In this cohort, vitamin D intake appears to be lower in those with frailty, with those with the lowest intake at higher risk of frailty, though this cannot be corroborated with actual deficiency. However, in broader terms nutritional intake and presence of nutritional deficiencies did not vary by or predict frailty status.

5.3 Physical activity

5.3.1 Introduction

Physical activity (PA) encompasses more than just exercise, including walking, leisure time, household, and occupational activities. PA has been shown to decrease as age [384,385] and level of frailty increase [386]. Lower levels of PA and longer durations of sedentary behaviours have been significantly associated with prevalent frailty, ADL disability and healthcare utilisation [386]. The influence of PA may be cumulative over the life course as there is some evidence demonstrating that higher leisure-time PA in midlife is associated with significantly lower prevalence of prefrailty and frailty in later life [387]. Additionally sedentary behaviour has been linked to decrease muscle mass and sarcopenia [388] and increased risk of incident frailty [389]. A similar trend was observed for successful ageing, which was significantly more likely in those with less sedentary behaviours and higher physical activity in mid- and later-life [390]. These findings along with a growing body of literature suggest that exercise interventions are safe and of potential benefit in healthy and frail older adults [391,392].

The role of PA and particularly exercise in PLWH has focused on its potential role in ameliorating some of the adverse effects of cART, such as negative changes in body composition, adverse metabolic profiles and cardiovascular risk, as well acting to reduce inflammation [393–395]. Reporting low PA is not uncommon in PLWH [396], especially in those with symptomatic disease [301]. In this study, we have reported that 47.8% of participants describe that their health limits them a lot in participating in strenuous activities. A study of physical functioning embedded within VACS showed that compared to HIV-negatives, PLWH (mean age 50) reported lower levels of exercise (p=0.03), faster age-related decline in function, and higher mortality for those with the lowest (HR 1.96; 95% CI 1.60-2.29) and intermediate (HR 1.37; 95% CI 1.13-1.65) tertiles of function [95]. In a US-based group of older adults (mean age 58.2; range 50-70) with well-treated HIV, higher self-reported levels of PA were associated with less neurocognitive impairment and higher functioning in ADLs compared to those with lower activity [397].

Multiple barriers to PA in PLWH have been reported including symptoms related to HIV, cART side effects, other medical conditions and age in general; as well

as poor motivation, low mood and lastly issues around competing priorities and cost of engaging in PA [398]. However, a number systematic review of RCTs of exercise interventions in PLWH show improvements in body composition, exercise capacity, cardiorespiratory fitness, muscle strength and health-related quality of life, whilst being safe and acceptable to patients [394,399,400]. Although specific research into PA in older adults with HIV is limited, based on results from older HIV-negative adults and younger PLWH, a combination of moderate/vigorous aerobic and resistance exercise for 20–40 minutes, 3 times per week has been advocated [401].

Section aims:

We aim to describe differing measures of physical activity within the cohort and any associations with frailty. We hypothesise that those with frailty will report lower levels of physical activity and have poorer performance on physical and functional measures compared to non-frail individuals.

5.3.2 Methods

We measured overall physical activity using the Physical Activity Scale in the Elderly (PASE) [201]. This self-report questionnaire, designed for use in epidemiological studies, included a range of physical activities that are more likely to be undertaken by older adults. Therefore, participants were asked about their engagement in a number household, occupational and leisure activities over the preceding 7-days. However, we asked participants to describe in relation to a 'normal week' to reflect usual behaviour.

Participants are asked about 12 activities including light, moderate and strenuous sport/recreational activities, muscle strengthening exercises, light and heavy housework, home repairs, light and heavier gardening, caring for another person, and working for either pay or as a volunteer. For recreational activities, frequency was defined in four categories of never, rarely (1-2days/week), sometimes (3-4days/week) and often (5-7days/week); as was duration of each activity at <1hour, 1-2hours, 2-4hours, >4hours. Household activities were rated as 'yes' or 'no' and occupation was recorded as number of hours and level of activity within that occupational role. Scores were derived by multiplying the weights associated

to frequency and duration of designated activities/occupation combined with the scores for the respective household activities. There are no units to the PASE score as it represents relative rather than absolute levels of PA. Total scores were derived and used in the analysis as a continuous variable and as percentile-based categorical variable.

The PASE was also used to assess exercise behaviour (none versus any), sedentary behaviour (>median number of hours of sitting based activity/week), and regular walking, with low activity taken to be walking outside the home or garden for any reason less than five days/week.

Other surrogate markers of physical activity were used to assess physical functioning including time taken to complete the 'timed get-up-and-go test' (TGUG) and the 5-times sit to stand test (5SST). To summarise the TGUG instructs participants that on the word 'go' that they should stand from the standard chair on which they are sat, walk at their usual pace to a predefined mark 3m from the chair where they are to turnaround and return to be seated in the chair. The test was timed from the word 'go' until the participant sits back down in the chair. Walking aids were permissible for this test. The test time (in seconds) was used as a continuous score and as a dichotomous variable with a cut-off at under or over 10-seconds, the latter of which being abnormal [402].

In the 5SST, participants were asked whether they could stand from a seated position to full standing without the use of their arms, being offered a practice attempt. If able, they were then asked to complete this activity 5-times, going from seated to full standing (with legs not touching the chair) and back to seated with no arm use. If arms were used the test was failed. The test was timed from the word 'go' until they sat down following the fifth stand. The time (in seconds) was used as a continuous variable. No abnormal cut point has been identified.

Additional parameters derived from the frailty phenotype, namely mean grip strength (in Kg) from the stronger hand and walking speed (in m/sec) were included as continuous variables.

5.3.3 Results

Table 5.12 describes participants' performance in physical activities divided by frailty status. All participants completed the PASE, with a median score of 150 across the cohort. Frail individuals had a significantly lower score of 79 compared to 173 in non-frail individuals (P<0.001). Those with frailty had significantly lower mean grip strength (p<0.001), slower walking speed (<0.001), slower time to complete the TGUG (p<0.001) and 5SST (p<0.001). A higher proportion of frail individuals took no regular exercise and walked less than five days a week. These associations were also demonstrated when the variables were examined by quintile, where for the PASE, 58.3% of those with frailty were in the bottom quintile compared to 10.7% of non-frail participants (p<0.001). Similar patterns were seen for the lowest quintile of grip strength (64.6% versus 19.8%, p<0.001) and walking speed (69.6% versus 8.8%, p<0.001). There was no difference in sedentary behaviour between the groups.

Negative scores or lower performance on all physical parameters predicted frailty, as can be seen in Table 5.13. A 1-point increase in PASE score was associated with a 2% reduction in frailty risk (aOR 0.98; 95%CI 0.97-0.99, p<0.001) and a linear trend was noted in relation to PASE with a 64% reduction in the odds of frailty for every quintile increase (aOR 0.36; 95%CI 0.23-0.54, p<0.001). Similar protective associations were seen for increases in grip, with a 78% reduction (aOR 0.22; 95%CI 0.13-0.38, p<0.001) and walking speed, with a 79% reduction in frailty likelihood per quintile increase (aOR 0.21; 95%CI 0.11-0.37, p<0.001). Taking no regular exercise other than routine walking and walking outside the home or garden less than 5 days/week were associated with a 3.8- and 2.5-fold increased odds of frailty respectively. Slower times to complete the TGUG and 5SST test were associated with an 84% and 34% increase in the odds of frailty respectively (p<0.001).

Table 5.12: Relationship between frailty and physical activity measures

	Full cohort N=253 (%)	Not frail N=205 (%)	Frail N=48 (%)	p-value [a]
PASE Score [b]	150 (106-214)	173 (126-234)	79 (50-117)	**<0.001**
PASE quintiles:				
22	50 (19.8)	22 (10.7)	25 (58.3)	**<0.001**
87	51 (20.2)	39 (19.0)	12 (25.0)	
137	50 (19.8)	45 (22.0)	5 (10.4)	
175	51 (20.2)	48 (23.4)	3 (6.3)	
228	51 (20.2)	51 (24.8)	0 (0)	
Mean grip (kg) [b]	38.3 (30.2-44.2)	40.2 (34.6-45)	26.3 (17.3-29.9)	**<0.001**
Grip quintiles:				
7.2	50 (19.8)	19 (9.3)	31 (64.6)	**<0.001**
28.0	51 (20.2)	39 (19.0)	12 (25.0)	
35.3	49 (19.4)	46 (22.4)	3 (6.3)	
40.5	52 (20.6)	52 (25.4)	0 (0)	
45.2	51 (20.2)	49 (23.9)	2 (4.2)	
Walk speed (m/sec) [c] (n=251)	1.11 (0.26)	1.17 (0.21)	0.80 (0.25)	**<0.001**
Walk speed quintiles				
0.15	50 (19.8)	18 (8.8)	36 (69.6)	**<0.001**
0.91	47 (18.7)	38 (18.5)	9 (19.6)	
1.06	53 (21.2)	51 (24.9)	2 (4.3)	
1.19	49 (19.4)	47 (22.9)	2 (4.3)	
1.32	52 (20.7)	51 (24.9)	1 (2.2)	
Walking <5days/week	87 (34.4)	58 (28.3)	29 (60.4)	**<0.001**
Sedentary behaviour	192 (75.9)	153 (74.6)	39 (81.3)	0.335
No regular exercise	111 (43.9)	76 (37.1)	35 (79.2)	**<0.001**
TGUG (secs, n=249) [b]	7.9 (6.8-9.8)	7.6 (6.6-8.8)	12.2 (10-16.2)	**<0.001**
TGUG >10 seconds	55 (22.1)	22 (10.7)	33 (75.0)	**<0.001**
5SST time (secs, n=225) [b]	13.3 (10.9-16.4)	12.8 10.6-15.3)	21.4 (16.5-27.5)	**<0.001**

[a] p-value based on Chi-squared test unless stated otherwise
[b] Median (IQR), p-value generated with MWU-test
[c] Mean (sd), p-value based on two-way t-test
TGUG- timed get up and go; 5xSST- 5-times sit-to-stand

Table 5.13: Association between frailty and markers of physical activity

	Association with frailty		
	aOR [a]	**95% CI**	**p-value**
PASE Score	0.98	0.97-0.99	**<0.001**
PASE [b]	0.36	0.23-0.54	**<0.001**
Mean grip (kg)	0.78	0.72-0.85	**<0.001**
Grip [b]	0.22	0.13-0.38	**<0.001**
Walk speed [b]	0.21	0.11-0.37	**<0.001**
Walking <5days/week	2.48	2.01-7.44	**0.022**
Sedentary behaviour	0.92	0.35-2.41	0.861
No regular exercise	3.85	1.68-8.84	**<0.001**
TGUG (n=249)	1.84	1.48-2.28	**<0.001**
TGUG >10 seconds	29.26	9.73-87.95	**<0.001**
5SST time (n=225)	1.34	1.19-1.52	**<0.001**

[a] Adjusted for age, sex, HADS score and comorbidity count
[b] Per quintile increase (linear trend)

Table 5.14 shows the performance on physical parameters across the three frailty categories. There is a significant decrease in physical activity, grip strength and walking speed going from robust to frail (all p<0.001) and an increase seen for time taken to complete timed tests (all p<0.001). Univariate analysis demonstrated that higher PASE, grip and walking speed predicted robustness compared to prefrailty and prefrailty compared to frailty, with the reverse association seen for slower times on the TGUT and 5SST (all p-values <0.001).

Table 5.14: Markers of physical activity across the three frailty groups

	Robust N=94 (%)	Prefrail N=111 (%)	Frail N=48 (5)	p-value [a]
PASE Score [b]	200 (145-275)	149 (108-198)	79 (50-117)	**<0.001**
Mean grip (kg) [b]	41.3 (37.7-45.9)	38.6 (31.2-44.1)	26.3 (17.3-29.9)	**<0.001**
Walk speed (m/sec) [c] (n=251)	1.26 (0.18)	1.10 (0.21)	0.80 (0.25)	**<0.001**
Walking <5days/week	22 (23.4)	36 (32.4)	29 (60.4)	**<0.001**
Sedentary behaviour	66 (70.2)	87 (78.4)	39 (81.3)	0.335
No regular exercise	29 (30.9)	47 (42.3)	35 (79.2)	**<0.001**
TGUG (n=249) [b]	7.1 (6.3-8.1)	7.9 (6.9-9.4)	12.2 (10-16.2)	**<0.001**
TGUG >10 seconds	4 (4.3)	18 (16.2)	33 (75.0)	**<0.001**
5SST time (n=225) [b]	11.5 (9.4-14.4)	13.3 (11.7-16)	21.4 (16.5-27.5)	**<0.001**

[a] p-value based on Chi-squared test unless stated otherwise
[b] Median (IQR), p-value generated with Kruskal-Wallis test
[c] Mean (sd), p-value based on one-way ANOVA

5.3.4 Discussion

We have demonstrated that in this cohort frailty was associated with lower physical activity (PA), and poorer performance on all included tasks of physical functioning including weaker grip, slower walking speed and longer times to complete the TGUG and 5SST. Sedentary behaviour did not vary between frail and non-frail groups and did not predict frailty.

We used the PASE as our measure of PA, which was statistically significantly lower in those with frailty, with a median score of 79 compared to 179 without, with a higher proportion of frail individuals in the lowest quintile of PASE scores at 58.1% compared to those without at 10.7%. A lower PASE was associated with frailty, with higher scores demonstrating a protective association, with a one-point increase in PASE associated with a 2% reduction in the odds of frailty. To put these findings in the context of the literature the original sample on which the PASE was constructed had a mean score of 103, and was derived from a population of community-dwelling older adults with mean age of 75 in whom frailty was not specifically screened for [201]. Later work in a group of sedentary adults with broader age-range showed an age differential, with a mean PASE of 144.2 (sd 75.8) in those aged 55-64 and 118.9 (sd 63.9) in those over 65, with lower

scores seen in women and those reporting chronic health conditions [403]. A Canadian community study examined PA using the PASE in 764 adults aged over 50, showing an overall mean PASE of 129.6 in men and 102.9 in women, which was higher in the younger groups at 154.3 and 137.9 in men and women respectively aged 50-64, which is the age group most closely resembling our cohort. Lower PASE was associated with higher age, female gender, living alone, not being partnered, lower education, lower income, medical comorbidity and depressive symptoms [384]. Other studies have demonstrated lower PASE scores in women and with increasing age [404,405]. Our overall cohort median is similar to the mean scores captured in studies in non-frail cohorts, particularly those including younger groups. The low PASE score amongst those with frailty is not surprising as we have demonstrated that they possess many of the predictors of lower PASE demonstrated above, particularly adverse socioeconomic characteristics, higher comorbidity burden and more commonly occurring symptoms of low mood. Additionally, though we used an alternative definition in assessing the low physical activity criterion for the FP it was highly prevalent at 48% of all recruited participants.

There is limited data on the use of the PASE in frailty research and none to our knowledge in the context of HIV. However, a German study of community-dwelling older adults with mean age 76 years showed that higher household based PA (i.e. chores, gardening, caring roles) on the PASE was associated with lower scores on a frailty index [406]. A US-study of 754, non-disabled, community-living persons aged 70 and older (mean 78.4) investigated the prognostic role of seven frailty predictors including the five from the FP. In this study, they used the PASE to define the low PA criterion, with scores of less than 64 and 52 in men and women taken to be low respectively resulting in 31% being identified as having low PA. Low PA was the strongest predictor of death in this cohort and was also independently associated with chronic disability and nursing home placement [112]. Interestingly these cut-offs are lower than the median seen in our frail cohort, which may be due the age difference between the cohorts with ours being broadly younger. Additionally, a Dutch case-control study investigating PA and sarcopenia in older adults (mean age 71, n=66 each group) showed the

PASE to be lower in those with sarcopenia at 148 compared to those without at 193 [376].

With respect to studies investigating frailty in PLWH, where the FP has been used to classify frailty a measure of low PA has been included, though how this is defined varies. Many use a proxy based on a variant of the question 'Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?' [166,175,176,180,181,190]. Others have used the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ) or a variant thereof, again using variable cut-offs for low PA [174,178,179]. The MLTPAQ provides a measure of PA in expended kilocalories/week, however none of the research groups have published this data to date making numerical comparisons difficult. Two US-based cross-sectional studies do comment on the role of PA in frailty in PLWH. Firstly, Erlandson et al. looked at a range of functional tools in PLWH, one of which was the FFP with the others being the short physical performance battery (SPPB) and 400m-walk. Low PA, defined as an energy expenditure of <500kcal/week measured using the MLTPAQ was one of the strongest predictors of functional limitation, on each of the three methods. Low PA was associated with 5.5-fold increase in the odds of having functional impairment, leading the authors to advocate a role for regular PA in maintaining functional independence [178]. Secondly, a pilot study of frailty by Sandkovsky et al. used a range of tools as proxies for the five FP phenotypic criteria and was the only study to evaluate an objective test of PA[186]. They used the Profile of Moods Scale (POMS) for self-reported PA and measured actual activity with a two-week period of actigraphy, which uses a wearable device to non-invasively monitor activity and rest. They showed no difference in PA measured by POMS or actigraphy between younger or older participants, but the objective measure did not correlate well to self-reported PA (Spearman=0.25, p=0.14), with self-report tending to overestimate activity[186].

The PASE score encompasses a range of physical activities from light recreational activity, to strenuous exercise, house and garden-based chores and occupational activity. Pulling out subsections of the PASE, avoiding the contribution from household chores and occupation, we show that taking no

regular exercise and walking outside the home or garden less than 5 days a week were both more common in those with frailty ($p<0.001$) and were both significantly associated with higher odds of frailty in multivariable analysis (aOR 3.9 and 2.5 respectively). Sedentary behaviour did not vary across the groups, making it potentially more important to consider time spent active rather than time spent on sedentary activities, such as watching television and seated based hobbies. However, reducing time spent on sedentary behaviours may still be beneficial as an investigation using NHANES data in those over 50 showed high levels of sedentary behaviour; with sedentary hours increasing and chance of meeting weekly recommended activity levels decreasing as frailty index increased [386].

The inclusion of occupational activity may have contributed to lower activity scores in those with frailty as we have already seen that frail individuals are significantly more likely to be retired or unemployed. Conversely it may help to explain the higher than average scores in the non-frail individuals, with alternative drivers being better overall health and functional ability allowing them to engage in PA or adopting a more proactive approach to personal health and well-being that drives them to remain more physically active.

The range of PA covered by the PASE is potentially important as it could mean that an increase in PA in any of these domains (i.e. household chores, walking, exercise) could potentially reduce the likelihood of frailty, however the non-discriminatory nature of the test in terms of its comprised range of activities cannot tell us which activity may be the most effective in frailty prevention or indeed how much of it one needs to do to maintain functional independence. It is suggested that mode of PA changes with age, with more PA spent walking and conducting home based ADLs rather than higher levels of exercise [407].

There are some limitations to our method of assessing PA. The PASE provides self-report data only, which is subjective compared to a more objective method such as using a pedometer or accelerometer to measure actual energy expenditure, however this was not practical in this small study and a recent systematic review showed no clear trend of under- or over-reporting PA by self-report versus direct measurement [408]. The PASE provides an arbitrary score, which though weighted on amount and strength of PA does not provide a

metabolic equivalent in kcal/week which can be gained from other tools such as the MLTPAQ and would potentially have provided useful information regarding energy imbalance when used alongside nutritional data. Additionally, there may be a social desirability to higher PA and as such participants may have overestimated their level of PA on the PASE. However, we see no reason to suggest differential reporting practices across the frailty groups and given the agreement between PASE scores and more objective markers of PA (grip, walk speed, timed tests), this is less likely to have had an impact.

We must interpret these findings with caution as participants may have low physical activity for many reasons. However, our multivariable model was used as before, allowing us to at least control for the effects of age, sex, symptoms of anxiety and depression and comorbidity number, but not nature. Again, the cross-sectional nature prohibits our ability to infer causality with respect to low physical activity and frailty and once again the relationship may be bidirectional, with declines in physical activity contributing to the development of frailty and the onset of frailty limiting one's ability to engage in physical activity, particularly activity that would be classed as physical exercise. It should be noted that the included markers of physical activity such as grip strength, slow walking speed, TGUG and 5SST may represent measures of physical functioning and as such are used as frailty biomarkers, with the first two used to define the criteria of weakness and slowness respectively in the FP used in this study. The latter two are used in alternative frailty screening tools; the Edmonton Scale for the TGUG [409] and The Study of Osteoporotic Fractures (SOF) scale for the 5SST [410]. A slow walking speed, taken as <0.8m/second or taking >5 seconds to walk 4m or a TGUG time of >10 seconds have good sensitivity but moderate specificity for frailty and have been advocated as two potential initial screening tools for frailty in clinical practice by the British Geriatrics Society [411].

These data represent a snapshot of PA reflecting current activity, which may be very different from other time points in that individual's life, so we cannot comment on the role of PA at the time of development of frailty, which may be important. There may be wider implication to low PA in this broadly middle-aged cohort as there is evidence to suggest that greater leisure time PA in mid-life is associated

with lower prevalence of frailty and prefrailty at a mean age of 74 [387] and stronger grip strength, a proxy for overall muscle strength at age 60-64 [412], possibly through amelioration of early age-related declines in muscle function. Furthermore, a systematic review of behavioural risk factors in mid-life identified 45 observational studies examining the effect of mid-life PA on ageing, demonstrating evidence that higher PA was associated with more successful ageing, less disability and functional impairment, slower cognitive decline, lower mortality, as well as reductions in cardiovascular disease, depression, and metabolic syndrome in later-life. Two studies investigated physical inactivity though failed to show any effect on later life outcomes [413].

This may be of great importance to this cohort, as we have demonstrated a gradation of PA in relation to frailty, with PA decreasing as frailty increased, with lower PA predicting higher frailty states, which was corroborated by looking at functional ability in terms of all the other physical parameters (grip, walking speed, time to complete TGUG and 5SST). Therefore, increasing PA could potentially halt or prevent progression to frailer states, which may be particularly relevant for those with prefrailty in middle-age.

5.3.5 Conclusion

Frail individuals report lower physical activity and exhibit poorer performance on measured physical activity tasks involving upper and lower limb function. Reduced activity and physical functioning was associated with higher frailty states. Therefore, in PLWH, physical activity warrants further investigation, including its exploration as a potential intervention in preventing or ameliorating frailty.

5.4 Blood-based biomarkers of inflammation and frailty

5.4.1 Introduction

PLWH are monitored closely within healthcare settings using numerous clinical and biochemical parameters to assess treatment efficacy, immune function and the effects of both HIV and its treatment on individual health status. These measures, along with novel markers of inflammation may reflect changes associated with the development of frailty or represent alternative ways of defining frailty states. These will be explored in this section.

The VACS index

The Veterans Aging Cohort Study (VACS) is a virtual cohort of patients engaged in the Veterans' Affairs healthcare system in the US recruited since 1997. The VACS index (VACSI) is a risk stratification tool based upon routinely collected HIV-parameters (CD4, HIV viral load) and laboratory blood tests (haemoglobin, platelets, creatinine, liver aminotransferases and hepatitis C status) [414]. These factors indicate bone marrow, renal, liver and immune system functioning and were shown to better reflect the interacting effects of HIV, ageing and physiological decline in relation to adverse outcomes in PLWH compared to HIV parameters alone [414]. The VACSI has been shown to correlate with pro-inflammatory state [415] and predict mortality (10% increase in 5-year mortality per 10-point increase in VACSI) [192,414]; hospitalisation [192]; cognitive impairment [416]; fragility fracture [417] and low functional status [159].

In a study by Akgün et al., the VACSI and an adapted frailty related phenotype were tested for their predictive ability for hospitalisation and 5-year mortality within the VACS cohort, demonstrating that the former had better predictive value compared to frailty [192]. The VACSI has also been shown to be associated with prefrailty and frailty using the five-criteria Fried model, where a 1-unit increase in the VACSI was associated with a 2.5% increase in the odds of prefrailty or frailty [418]. Lastly the VACSI has been shown to be associated with poor exercise capacity and weak grip and lower limb muscle strength based on a cross-sectional study of 55 well-treated PLWH with mean age 52.3 promoting its role as a measure of loss of physiologic reserve and possible potential to predict disability [419].

Routinely collected blood parameters

Abnormalities in routine laboratory blood parameters have been associated with adverse outcomes in older adults with and without HIV, in many contexts, including frailty. Interest in their predictive value in PLWH has led to their inclusion in risk stratification models such as the VACSI as described above. Within the development of the VACSI, haemoglobin, alongside markers of liver and renal function correlated with inflammation and mortality [415]. Additionally in patients commencing cART within the UK-CHIC cohort, lower levels of haemoglobin (Hb) and albumin, and higher levels of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were associated with short term mortality [420].

In PLWH, lower Hb levels have been demonstrated at older ages [56] and have been associated with both prevalent and incident prefrailty and frailty, with researchers suggesting that low haemoglobin could be implicated in the pathogenesis of HIV-related frailty [418].

In older HIV-negative adults, lower Hb [421,422] low albumin [162,423], lower lymphocyte and higher neutrophil counts are predictive of higher frailty states [424]. In addition, a frailty index comprising of biomarker data including these above parameters predicts mortality in the oldest old (>85), performing better than a usual clinical deficit frailty index at lower scores, possibly suggesting identification of frailty at an earlier, subclinical stage [425].

Pro-inflammatory markers

It is suggested that chronic low grade inflammation is a key feature in ageing tissues and age-related diseases, with considerable focus now being placed on the concept of 'inflammaging' [151]. Like frailty, the drivers of inflammaging are multiple and multi-system, including accumulation of protein and cellular damage, immune dysregulation, cellular and immunosenescence, activation of the coagulation system and chronic infections, particularly CMV [426]. It has previously been discussed how cytokines and markers associated with inflammation have been shown to increase with age, with elevations seen in frail individuals with [159,160] and without HIV [161,162]. In PLWH it has been speculated that inflammation may signify a common connection between HIV, ageing and frailty [427].

Those of particular interest are IL-6, CRP and TNF-α, which have been found to be elevated in those with [427] and without HIV [162,424]. Higher IL-6 levels have been associated with increasing age [428]; HIV-positive serostatus and particularly increased viral load and decreased CD4 [156]; lower physical activity [159,429]; age-related functional decline [430] and frailty in individuals with [160] and without HIV [161,421,431]. CRP levels have been shown to be higher in those with HIV [432] and frail people without [422–424,431]. Both IL6 and CRP predict mortality in PLWH [153,433] and HIV-negative older adults [152].

5.4.2 Methods

Routine laboratory parameters

All participants gave consent allowing access to their medical records including laboratory parameters. Data was collected on their most recent (within 6 months of baseline visit) routine laboratory parameters focussing on:

Full blood count with haemoglobin (Hb) in g/L, white blood cells and differential (neutrophils and lymphocytes) and platelets recorded as cells x 10^9/L. Anaemia was defined based upon WHO (World Health Organisation) criteria taking Hb level cut-offs below 13 g/dL in men and 12 g/dL in women.

Creatinine measured in μmol/L and the associated estimated glomerular filtration rate (eGFR) which was reported in continuous forms for values < 60 and as ≥60 for all other values. Therefore, the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) estimation of eGFR was calculated for each participant. This estimated GFR using the serum creatinine plus age and ethnicity (black versus non-black ethnicity) [434].

Liver function parameters, including albumin (g/L), alkaline phosphatase (IU/L), alanine aminotransferase (ALT) (g/L) and aspartate aminotransferase (AST) (g/L) were recorded. Most laboratories only reported one of the above aminotransferases, with both required to calculate the VACS index as described below therefore all participants consented to provide a fresh-serum sample for a full liver function test to be performed. Where haemolysis of either ALT or AST occurred, the respective present value was used to calculate the VACSI. There were no examples of both being haemolysed.

The VACS index

The VACS index is a weighted composite score designed to be a marker of general systems injury combining age alongside HIV and routinely collected laboratory data including CD4 count, HIV-1 RNA, Hb, platelets, AST, ALT, creatinine and Hepatitis C status [414]. Creatinine was used to calculate the GRF and a composite marker of liver fibrosis called the FIB-4 was computed using the equation:

- FIB-4 = [(years of age x AST)/(platelets in 100/L X $\sqrt{AST}$)]

Table 5.15 shows the scoring for the constituent factors. VACSI was treated as a continuous variable and assessed by 10-point increase.

Pro-inflammatory cytokines

All participants consented to provide a blood sample, which was separated into plasma and cell pellet components and stored at -80°C. Commercially available kits (V-plex, Meso Scale Discovery, Rockville, Maryland USA) were utilised to measure cytokine levels. Each assay employed plates pre-coated with capture antibody to which the plasma samples and then detection antibody were added as per the product protocol, with cytokine values obtained via electrochemoluminescence.

Cytokines and their respective detection values were, IFN-γ: 0.20–938 pg/ml; IL-6: 0.06–488 pg/ml; TNF-α: 0.04–248 pg/ml and CRP: 1.33–49 608 pg/ml. All measurements used first-time thawed plasma samples and were performed in duplicate, with mean values used for analysis. Values were excluded if they were outside of the given detection range or where duplicate measurements varied by greater than 15%.

252/253 (99.6%) participants provided blood samples for storage and biomarker analysis. After exclusion of samples with greater than 15% variance between duplicate samples and those values below the detection range for the respective inflammatory biomarker, data were available for 248/252 (98.4%) for CRP (202 non-frail, 46 frail); 235/252 (93.3%) for IFN-γ (190 non-frail, 45 frail); 188/252 (74.6%) for IL-6 (150 non-frail, 38 frail) and 241/252 (95.6%) for TNF-α (196 non-frail, 45 frail).

Table 5.15: VACSI constituents and scoring method

Factor	Category	Score
Age	<50	0
	50-64	12
	≥65	27
CD4, cells/mm^3	≥500	0
	200-499	6
	100-199	10
	50-99	28
	<50	29
HIV-1, copies/ml	<500	0
	500-1x10^5	7
	≥1x10^5	14
Hb, g/dl	≥14	0
	12-13.9	10
	10-11.9	22
	<10	38
FIB-4	<1.45	0
	1.45-3.25	6
	>3.25	25
eGFR, ml/min	>60	0
	45-59.9	6
	30-44.9	8
	<30	25
Hepatitis C	Present	5

5.4.2.4 Cytomegalovirus

A serum sample was analysed in the Royal Sussex County Hospital laboratory for the presence of anti-cytomegalovirus (CMV) IgG indicating the presence or absence or prior infection. For those with a positive IgG, arbitrary anti-CMV IgG units (AU/ml) were provided as a surrogate marker of CMV activity. This approach that has been used in previous frailty work in a population of patients engaged in old age psychiatry services [435]. These arbitrary units were recorded as continuous values <250 and ≥250 for all other values. These were dichotomised to <250AU/ml to summarise low CMV activity and ≥250 as high activity.

5.4.3 Results

VACSI, CMV and laboratory parameters.

Table 5.16 shows the relationship of what might be considered more routine laboratory blood biomarkers and frailty. As all participants were aged 50 years

and over the minimum VACSI score for the cohort was 12. Those with frailty had a statistically significantly higher median VACSI score at 25.5 compared to 18 in those without (p=0.043). Haemoglobin levels were significantly lower in the frail group (p=0.043), however the absolute mean difference was only 0.4g/dl. Though anaemia was more common in frail individuals (10.4 versus 5.9%), this difference was not significant. There were no differences in white cell or platelet count, markers of liver function, creatinine or GFR. In this cohort, 95% were positive for CMV with no difference between the frailty groups. CMV activity was assessed using arbitrary anti-CMV IgG units dichotomised to <250 and ≥250 representing lower and higher CMV activity respectively. Here, there was some evidence that those with frailty had a larger proportion with higher CMV activity compared to non-frail (93.3 versus 81.0; p=0.043).

Univariate and multivariable logistic regression using the previously described model controlling for age, sex, number of comorbidities and HADS score were undertaken for the VACSI, CMV parameters and each of the described routine laboratory tests. In univariate analysis, only VACSI was associated with frailty, with a 1-point increase in VACSI was associated with a 3% increase in the odds of frailty (95% CI 1.01-1.06, p=0.013) but this association did not persist in multivariable analysis. Only platelet count showed a significant association with frailty in multivariable analysis, exerting a protective effect with increasing platelet count (aOR 0.99; 95% CI 0.98-0.99, p=0.013). Data not shown further, but can be found in Appendix 4, Table A4-1.

Table 5.16: Relationship between the VACSI and laboratory parameters and frailty status

	Full cohort	Non-frail	Frail	p-value[a]
VACSI [b]	22 (18-33)	18 (18-28)	25.5 (18-38)	**0.043**
Haemoglobin [c]	14.7 (1.46)	14.8 (1.39)	14.4 (1.73)	**0.043**
Anaemia [c]	17 (6.7)	12 (5.9)	5 (10.4)	0.256
WCC [c]	6.5 (2.0)	6.5 (2.0)	6.3 (2.1)	0.475
Neutrophils [b]	3.1 (2.5-4.1)	3.1 (2.5-4.1)	3.3 (2.3-4.4)	0.843
Lymphocytes [b]	2.1 (1.7-2.8)	2.2 (1.7-2.8)	2.0 (1.6-2.8)	0.461
Platelets [c]	222 (66)	225 (67)	209 (61)	0.119
Albumin [c]	46.5 (4.5)	46.8 (4.7)	45.5 (3.3)	0.081
ALT [b]	26 (20-33)	26 (20-33)	23 (17-38)	0.514
AST (n=239) [b]	25 (20-31)	24.5 (20-30)	25 (21-36)	0.071
ALP [b]	83 (67-104)	83 (67-104)	81 (68.5-103.5)	0.997
Creatinine [b]	89 (77-100)	90 (77-100)	84 (72-101)	0.190
GFR estimation [c]	79.6 (16.4)	79.3 (16.3)	81.2 (16.9)	0.463
CMV positivity	241 (95.3)	196 (95.6)	45 (93.8)	0.585
Anti-CMV IgG low	40 (16.7)	37 (19.0)	3 (6.7)	**0.046**
Anti-CMV IgG high	200 (83.3)	158 (81.0)	42 (93.3)	

[a] p-value based on Chi-squared test unless stated otherwise
[b] Median (IQR), p-value generated with MWU-test
[c] Mean (sd), p-value based on two-way t-test

When examining the same blood parameters and VASCI across the three frailty groups of robust, prefrail and frail we demonstrated no significant differences in any parameter. However, there were trends for increasing VASCI (p=0.061), decreasing haemoglobin (p=0.064) and increasing proportions of participants with higher CMV activity (p=0.066) with increasing frailty status. This is shown in Table 5.17.

Table 5.17: Relationship between VACSI and laboratory parameters across the three frailty categories

	Robust	Pre-frail	Frail	p-value [a]
VACSI [b]	18 (12-27)	22 (18-33)	25.5 (18-38)	0.061
Haemoglobin [c]	149.5 (12.7)	147.1 (14.7)	143.5 (17.3)	0.064
WCC [c]	6.4 (1.8)	6.7 (2.1)	6.3 (2.1)	0.408
Neutrophils [b]	3.0 (2.5-3.9)	3.3 (2.5-4.1)	3.3 (2.3-4.4)	0.687
Lymphocytes	2.1 (1.7-2.7)	2.3 (1.7-2.9)	2.0 (1.6-2.8)	0.548
Platelets [c]	225.5 (61.8)	225.2 (71.8)	208.7 (61.6)	0.296
Albumin [c]	46.7 (2.7)	46.9 (5.9)	45.5 (3.3)	0.210
ALT [b]	27 (19-33)	26 (20-32)	23 (17-38)	0.856
AST (n=239) [b]	25 (20-31)	24 (20-28)	25 (21-36)	0.160
ALP [b]	81.5 (67-106)	85 (67-103)	81 (68.5-103.5)	0.866
Creatinine [b]	87 (77-99)	92 (78-102)	84 (72-101)	0.152
GFR by CKD-epi [b]	82.0 (14.4)	77.0 (17.5)	81.2 (16.9)	0.071
CMV positive	90 (95.7)	106 (95.5)	45 (93.8)	0.859
Anti-CMV IgG low	20 (22.5)	17 (16.0)	3 (6.7)	0.066
Anti-CMV IgG high	69 (77.5)	89 (84.0)	42 (93.3)	

[a] p-value based on Chi-squared test unless stated otherwise
[b] Median (IQR), p-value generated with MWU-test
[c] Mean (sd), p-value based on two-way t-test

Pro-inflammatory markers

Table 5.18 shows the median values for each of the biomarkers for the full cohort and between those with and without frailty. The median IL-6 level was significantly higher in those with frailty compared to those without at 1.4pg/ml and 0.9pg/ml respectively ($p<0.001$). CRP was also higher amongst frail individuals but this failed to reach statistical significance ($p=0.215$). There was no difference in levels of IFN-γ or TNF-α.

Table 5.18: Levels of inflammatory markers by frailty status

Median (IQR)	Full cohort	Not frail	Frail	p-value [a]
CRP (mg/ml)	4.11 (2.23-9.08)	3.78 (2.19-8.97)	6.22 (2.62-10.75)	0.215
IFN-γ (pg/ml)	7.90 (5.40-12.77)	7.97 (5.62-12.32)	7.89 (4.88-16.07)	0.722
IL-6 (pg/ml)	1.03 (0.72-1.63)	0.99 (0.63-1.42)	1.40 (0.96-2.01)	**<0.001**
TNF-α (pg/ml)	3.76 (2.62-5.03)	3.77 (2.43-5.04)	3.76 (2.83-5.03)	0.987

[a] p-value generated using the MWU-test

Table 5.19 shows the univariate and where appropriate multivariable associations between frailty and the measured inflammatory markers per unit and quintile increases. Owing to a reduction in frail participants in each group, sex was removed from the multivariable model, based on its weaker contribution to model strength. IL-6 was the only pro-inflammatory cytokine associated with frailty in this cohort when examined by quintile rather then 1-unit change in IL-6 level. There was a linear relationship demonstrated between increasing IL-6 and increased odds of frailty with a 53% increased likelihood for every quintile increase in IL-6 after controlling for age, number of comorbidities and HADS score (p-value for trend 0.018).

Table 5.19: Associations between frailty status and markers of inflammation

		Association with frailty		
Biomarker	**Crude OR (95% CI)**	**aOR [a]**	**95% CI**	**p-value**
CRP	1.02 (1.00-1.03)	1.01	0.99-1.02	0.537
CRP (quintile) [b]	1.07 (0.41-2.82)			
IFN-γ	1.02 (0.99-1.04)	1.02	0.99-1.05	0.166
IFN-γ (quintile) [b]	1.12 (0.44-3.18)			
IL-6	1.19 (0.98-1.44)	0.94	0.76-1.17	0.585
IL-6 (quintile) [b]	8.27 (1.75-39.08)			
IL-6 trend/quintile	1.64 (1.22-2.19)	1.53	1.07-2.19	**0.018**
TNF-α	1.02 (0.87-1.20)	0.96	0.79-1.17	0.688
TNF-α (quintile) [b]	1.09 (0.36-3.28)			

[a] Adjusted for age, HADS score and comorbidity count
[b] Comparing highest to lowest quintile

Table 5.20 shows the distribution of pro-inflammatory cytokines across the three frailty categories. Median values of both CRP and IL-6 increased with frailty state from robust to frail (p=0.012 and p<0.001 respectively). Again, there was no relationship with IFN-γ or TNF-α.

Table 5.20: Measures of inflammation across the three frailty categories

Median (IQR)	Robust	Prefrail	Frail	p-value [a]
CRP (mg/ml)	3.16 (1.82-6.42)	4.71 (2.52-12.54)	6.22 (2.62-10.75)	**0.012**
IFN-γ (pg/ml)	7.73 (5.62-13.09)	8.49 (5.40-12.04)	7.89 (4.88-16.07)	0.932
IL-6 (pg/ml)	0.88 (0.54-1.21)	1.03 (0.71-1.75)	1.40 (0.96-2.01)	**<0.001**
TNF-α (pg/ml)	3.66 (2.47-4.80)	3.97 (2.39-5.23)	3.76 (2.83-5.03)	0.763

[a] p-value generated with Kruskal-Wallis test

5.4.4 Discussion

VACSI

The median VACSI index score was significantly higher in those with frailty compared to those without (25.5 versus 18, p=0.043) and though VACSI score increased as frailty state increased (robust, prefrail, frail) there was no significant difference across the groups (p=0.061). The VACSI was not associated with frailty in multivariable analysis. One study of 303 well-treated PLWH with median age 48 and 76% male gender demonstrated an association between frailty status and VACSI. Here, in the Study to Understand the Natural History of HIV/AIDS (SUN) the pooled frail and prefrail individuals had a median VACSI of 18 (IQR 10-22) compared to 10 (IQR 6-18) if non-frail (p<0.001); with a 1-unit increase in VACSI associated with a 2.5% increase in the odds of being prefrail or frail (aOR 1.025; 95%CI 1.004-1.046, p=0.019) after adjusting for ethnicity, employment and depression [418]. They proposed that the VACSI could be used to identify prefrailty/frailty though they do not offer any suggested cut-offs for diagnosis [418]. Akgün et al. examined the predictive value of the VACSI and an adapted FP (aFP) on adverse outcomes associated with frailty in those enrolled in VACS. Here the median VACSI score for HIV-negative participants was 12 (IQR 6-23), which is lower than the values seen across our cohort where median VACSI was 22 (IQR 18-33), but similar to those with HIV with undetectable viral load in

Akgün's work where the median VACSI was 23 (IQR 12-38); though the equivalent frailty prevalence (based on a 4-item aFP) was 2.0%. It should be noted that the VACS cohort was broadly younger (mean age 50), with less ART coverage (70%) and higher hepatitis C prevalence. Additionally, the VACSI was designed as a risk prediction tool for adverse outcomes of frailty rather than for frailty itself with the authors conceding that its construct does not map well to the frailty phenotype but is more in keeping with the deficit accumulation model of the frailty index, representing an objective measure of physiologic vulnerability, which they consider to be frailty [192]. This potential disconnect between the FP and the VACSI may be why we failed to show an association between the two. Alternatively, it may be that in our well treated cohort the frail and non-frail groups are similar in terms of the blood-based parameters that are used to calculate the VACSI as we saw no significant difference in any of the scoring criteria (age, Hb, platelets, ALT, AST, creatinine, CD4 and VL) and we had a very low prevalence of hepatitis C. The role of the VACSI in predicting adverse outcomes alone and in relation to frailty does still warrant further investigation as the use of a blood-based vulnerability index that can be generated from routine clinical data could be appealing in clinical practice.

Routine laboratory blood markers:

We saw no significant differences in any of the routinely measured blood parameters and frailty status in this study. In multivariable analysis, higher platelet count was associated with lower odds of frailty (aOR 0.99; CI 0.98-0.99, p=0.013) though an explanation for this association is not clear. Mitnitski et al. did show an association with low platelets and adverse risk profile, prompting its inclusion in their biomarker based FI [425]. However, others have reported no association between frailty and platelet count [421], and It is possible that it is a chance finding, which may warrant re-evaluation in a larger study. We showed a trend of decreasing haemoglobin with increasing frailty state though this failed to reach statistical significance. In those with HIV low haemoglobin [185,189,418] and low albumin [180] have been associated with frailty where it has been hypothesised to reflect changes associated with chronic inflammation, which is often cited in frailty pathophysiology.

CMV:

There was high prevalence of prior CMV infection with 95% of participants positive for CMV antibodies, which was not different between those with and without frailty. Using arbitrary IgG units as a marker or CMV 'activity' we demonstrate that those with frailty were significantly more likely to have higher CMV activity (p=0.046) with a non-significant trend seen with increasing proportion with higher CMV activity as frailty state increased.

The relationship between CMV and frailty has been examined in the Women's Health and Ageing Study where CMV positivity was associated with a higher risk of both prevalent [436] and incident [437] frailty. This was mediated by IL-6 with those with CMV positivity and high IL-6 at the greatest risk or both frailty and prefrailty. Prevalence of frailty has also been shown to increase with increasing anti-CMV IgG concentration [437]. Others have shown no association with CMV seropositivity and frailty [424]. In HIV settings, where CMV seropositivity tends to be higher than the HIV-negative population, it has been associated with a higher risk of non-AIDS events and non-AIDS related deaths [438] though frailty has not been examined to our knowledge.

CMV, a member of the herpes virus, manages to evade host immune mechanisms resulting in lifelong infection with viral dormancy accompanied by episodes of viral reactivation. It is suggested that higher anti-CMV IgG titres may reflect a higher number or more prolonged periods of reactivation, which in turn may drive chronic inflammation [437]. It should also be noted that anti-CMV IgG implies past infection, the duration and subsequent activity of which is unknown. It is possible that individuals became CMV-positive following their transition to a frail state and as such it may not have played a role in its development. In the future CMV vaccination or eradication strategies could be investigated as an intervention to reduce inflammo-ageing, early immunosenescence and ultimately frailty.

Markers of inflammation

Of the proinflammatory cytokines investigated only IL-6 showed an association with frailty. IL-6 levels were significantly higher in frail compared to non-frail individuals (1.40 vs 0.99pg/ml, p<0.001) and increased as frailty state increased

at 0.88pg/ml in robust, 1.03 in prefrailty and 1.40 with frailty (p<0.001). In multivariable analysis, a quintile increase in IL-6 was associated with a 53% increase in the odds of frailty. CRP was also higher in those with frailty compared to those without but only reached statistical significance in three group comparisons (p=0.012). Increased CRP did not predict frailty however and there was no association between frailty and TNF-α or IFN-γ in any analysis.

Inflammatory cytokines have gained increased attention in HIV and particularly in issues of HIV and ageing. Levels of CRP and IL-6 have been shown to be higher in PLWH [427,439] and have been associated with AIDS events [440,441], and immune reconstitution inflammatory syndrome and death following cART initiation [440]. IL-6 is the most consistently reported cytokine related to adverse outcomes in PLWH with a large cross-sectional study pooling data from three cohorts (N=9864) reporting that higher levels of IL-6 were associated with older age, higher BMI, lower education, non-black ethnicity, detectable VL, lower nadir CD4, PI use, smoking and comorbid conditions [157].

There have been mixed findings with respect to any association between inflammatory biomarkers and frailty or low functioning in PLWH, with the strongest relationship seen for higher IL-6. A cross sectional study of 80 HIV-positive individuals (mean age 52.8) classified as high (n=49) or low (n=31) function, including frailty, showed that those with low function had higher levels of IL-6 at 2.2 versus 1.0pg/ml, as well as higher TNF-α (2.1 versus 1.5pg/ml) and hsCRP (2.2 versus 1.6μg/ml). However, only IL-6 was significantly associated with low function with a 0.1 log increase associated with a 20% increase in the odds of low function after controlling for CD4, smoking status and viral hepatitis (aOR 1.20; 95% CI 1.02-1.51). TNF-α and hsCRP were not associated with higher likelihood of low function [442]. Another small US study of 21 individuals (mean age 59.7), with well-controlled HIV and 10 community controls showed significantly higher levels of IL-6 (2.10 versus 0.42pg/ml; p=0.003), CRP (4582 versus 650ng/ml; p<0.001) and senescent CD4 and CD8 T-cells in those with HIV yet there was no association with lower functional ability [427], which was also seen with respect to IL-6 in another cross-sectional study of HIV-positive women [158].

The ALIVE study of those with previous or current IVDU showed median IL-6 to increase with increasing frailty state at 1.44, 1.64, and 1.90pg/ml if robust, prefrail and frail respectively, which in multivariable analyses adjusting for sociodemographics, depressive symptoms, number of comorbidities, and HIV status, an increasing IL-6 (log SD) was significantly associated with frailty (aOR 1.33; 95% CI, 1.09–1.61) and mortality (aHR1.38; 95% CI 1.19-1.59) [160]. However, only 29% had HIV and those with HIV had a lower risk of mortality in relation to inflammatory profiles than those without [160]. The AGEhIV study showed higher CRP in those with HIV compared to those without though it was not associated with higher frailty states [190]. Again, though Sandkovsky et al. examined frailty in a group with HIV they only reported the relationship with inflammatory markers and age, showing no significant differences with age in IL-6, CRP or TNF-α [186].

In non-HIV settings, IL-6, TNF-α, and CRP have been linked to frailty, particularly at great age [443]. Data from the Newcastle 85+ study of frailty in the very elderly showed seven biomarkers to be associated with frailty when measured by the Fried FP or the Rockwood FI, which were basal IL-6, basal TNF-α, CRP, albumin, neutrophil count, lymphocyte count, and memory/naïve CD8+ cell ratio. Using the FP, 21.6% were frail and 60.3% prefrail with low IL-6 protective for higher frailty states (OR 0.48; 95% CI 0.31-0.74) as was low TNF-α (OR 0.59; 95% CI 0.38-0.90), with high CRP being predictive of frailty (OR 1.82; 95% CI 1.19-2.80). Though inflammation appears to be important in the pathogenesis of frailty in this very elderly cohort they showed no association with CMV seropositivity nor associations with markers of immunosenescence or cellular ageing such as oxidative stress, telomere length and DNA damage [424]. Additional studies in those over 80 have demonstrated increasing frailty to be associated with higher IL-6 [161,162], CRP [162,444] and TNF-α [162]. In a longitudinal study IL-6 increased with age and higher levels were associated with a significant decrease in grip strength and walking speed, cardinal features of frailty [430].

IL-6 is involved in acute inflammation, having both a pro- and anti-inflammatory effect, which triggers and then limits the inflammatory response. However, in some situations there is chronic elevation of IL-6, such as in immune-mediated

disease, HIV and older age [445]. What provokes the conversion from acute to chronic activation is unknown as is whether the elevation is a response to try and suppress an abnormally long period of inflammation or a primary driver of proinflammatory state through excessive activation, hence the current inability to infer causation, which is the case here with our cross-sectional data. Other limitations include the fact that all blood sampling was done on one occasion at the time of baseline visit and as such reflects the current physiological environment at that point in time meaning we cannot reflect on trends over time or markers of body physiology at the point of transition in to frailty, which may be more important. The lower levels of inflammatory markers overall may reflect the younger age of our cohort as well as the well-treated nature of their HIV. The variance on measures of IL-6 was higher than all the other cytokines for unknown reasons as they were prepared in the same manner using a multiplex assay which tests for the cytokines on the same sample. It is possible that had we had full data the association between IL-6 and frailty could have been stronger or indeed weaker. However, we had data for 79.2% of frail participants and 73.2% of non-frail, and the association persisted after controlling for age, number of comorbidities and HADS score with the findings generally in keeping with the research literature.

5.4.5 Conclusion

Of the tested inflammatory markers, only IL-6 was significantly higher with increasing frailty states and associated with a higher likelihood of frailty in multivariable analysis. This is in keeping with the literature in HIV-negative individuals and adds to the predictors of frailty in PLWH, supporting the role of proinflammatory pathways.

5.5 Chapter summary

We have examined a broad range of potential biological predictors of frailty based on the theorised cycle of frailty, which introduces potential pathways to the pathogenesis of the frailty syndrome. We have demonstrated a role for sarcopenia, sarcopenic obesity, low vitamin D intake, low physical activity and poorer performance on tasks of strength and function and the pro-inflammatory cytokine IL-6. This constellation of predictors is interesting as they can be seen to be interrelated in that low physical activity and low vitamin D may have deleterious effects on skeletal muscle, particularly in the face of age related loss of muscle mass, with sarcopenia likely to result in poor physical performance and potentially earlier muscle fatigue. This could contribute to all the frailty phenotypic criteria. IL-6 originates from skeletal muscle and adipose tissues and its chronic activation is thought to have a negative effect on muscle function potentially though suppression of insulin-like growth factor-1 (IGF-1), which may promote sarcopenia [445]. These findings are in keeping with hypothesised pathophysiological processes of frailty, particularly in the context of the frailty syndrome suggesting that frailty is occurring in the same way in those with HIV as those without and that the premature occurrence may be in part due to the HIV virus or its treatments having negative effects on these key frailty drivers.

Future directions

The findings from this study are broadly, as mentioned, in keeping with the published literature but do provide further insights in the context of frailty in those with HIV, which has not always been explicit in past work. Most research in the area is observational and cross-sectional in nature so it will be imperative to explore these credible candidates for pathophysiological drivers of frailty in longitudinal studies, ideally from the time of HIV diagnosis. This would allow one to track changes induced by cART, ageing, and other unknown factors alongside their role on frailty and functional trajectories. Ultimately, this kind of approach will be needed to strengthen potential aetiological links and provide a basis for further interventional work in such areas as physical activity or reducing inflammation.

Chapter 6 Psychosocial and cognitive determinants of frailty

6.0 Introduction

As HIV has evolved into a chronic manageable disease the majority of those affected are surviving to older ages in line with the HIV-negative population. Consequently, as discussed, there has been increasing interest in issues of ageing in this cohort including non-infectious comorbidities, frailty and functional decline. However, focussing on this biomedical perspective on ageing in HIV and in ageing more broadly is too narrow and a comprehensive biopsychosocial view is necessary to see the bigger picture, which is evidenced by the broad body of literature that now exists examining psychological, social and cognitive aspects of ageing in PLWH [446].

The lack of consensus definition of frailty has meant that many tools have been developed to attempt to classify frail individuals to identify those most at risk of adverse outcomes. The Fried phenotype (FP) model employed in this study utilises markers of frailty that serve as criteria in their rule-based system. However, the factors used in defining the FP are said to be unit-dimensional, representing physical attributes whilst neglecting the role of cognitive, psychological and social factors, which in themselves have been related to negative health outcomes. Therefore, declines in psychosocial functioning may be a risk factor for age-related decline alongside physical frailty, which may overlap in their influences upon each other [447]. In earlier chapters, we have already demonstrated significant relationships between markers of socioeconomic status and frailty such as financial disadvantage, employment and housing as well as the association with depression, anxiety and cognitive functioning.

Reviews of frailty indeed define it as a multi-dimensional construct resulting from the interaction of physical, psychological, social and environmental factors [448]. In line with this there have been calls for the inclusion of psychosocial [447,449,450], cognitive and mood parameters [108,112,451,452] in frailty assessment strategies. Additionally, across the literature we have seen the emergence of the use of

terms such as social [280,449], psychological and cognitive frailty [449,453]. Multidimensional frailty assessment tools do exist such as the Rockwood frailty index that includes a variety of variables deemed deficits, drawn from a range of signs, symptoms, diagnoses and functional deficits, which have included cognitive, mental health and social situation [110,454]. Another is the Tilberg Frailty Index (TFI), which defines frailty as a dynamic state affecting those experiencing deficits in one or more domains of human functioning, namely physical, psychological (memory, depression and anxiety, coping ability) and social (living alone, social relations and social support) [455,456]. A comparison of the FP and TFI shows moderate correlation (r=0.483) although they identify different frailty populations, as the prevalence was significantly higher using the TFI compared to the FP at 44.6% and 12.7% respectively in a sample of 276 community-dwelling Italian older adults (mean age 73.4) [457]. The use of physical, psychological and social frailty domains may indeed find differing frailty populations. A cross-sectional study using the TFI showed that each domain had different predictor variables, though the authors still advocate dividing frailty into distinct domains to get the most accurate picture of frailty determinants [456]. The role of multi-dimensional tools in improving frailty detection and predicting adverse outcome is not so clear cut however. In a study of physically frail older adults (mean age 78.1), social, psychosocial or cognitive frailty as assessed by domains within the Groningen Frailty Indicator did not improve the prediction of adverse outcome and were not related to disability, quality of life or hospital admission [458].

Having chosen the FP as the frailty assessment tool, we were mindful of the potential for influence, be that predictive or protective, of cognitive and psychosocial factors on the occurrence of frailty within this cohort, which we sought to investigate further. Therefore, this chapter comprises two sections; the first of which will address the psychosocial aspects of frailty within this study, with the second focussing on cognitive factors.

Chapter aims:

The aims of this chapter are to:

- Describe markers of psychosocial functioning, focussing on social networks, purpose in life, grit and quality of life in the full cohort and by frailty status.
- Describe cognitive performance on broad cognitive screening tools and specific neuropsychological tests in relation to frailty status.
- Examine the associations between psychosocial and cognitive factors and the occurrence of frailty.
- Investigate whether psychosocial and cognitive parameters exhibit trends across the frailty spectrum, with particular reference to those in the prefrail state who may be at the highest risk of transition to frailty.

6.1 Psychosocial determinants of frailty

6.1.1 Introduction

Ageing is a diverse process with a great deal of heterogeneity in terms of ageing trajectory and individual response to challenges, stressors or overt stress events that inevitably accompany ageing and being older. Many of these stressors involve loss, including retirement or a move away from key societal roles, which may additionally result in loss of status, income and a sphere of social contacts. There may be health losses through chronic illness, sensory loss, functional losses and disability. This may also limit one's independence and may alter the life-space, i.e. the physical and psychological environmental, in which they exist. Bereavement is more common, with loss of spousal partners, family members and core social contacts, causing shrinkage or contraction of social networks. Cognitive loss, be that mild cognitive impairment or overt dementia may challenge all the above.

Receiving a diagnosis of HIV may be considered a significant life-stressor event and may be associated with a considerable number of additional psychosocial stressors. These may include living with HIV as a chronic disease; changes in appearance due to cART; ongoing background risk behaviours such as drug and alcohol misuse; stigma, political and legal disadvantage due to HIV, sexual orientation, age, ethnicity or immigration status; as well as uncertainty about the

future particularly regarding the prospect of premature morbidity and mortality from HIV [7,102,459–462].

Psychosocial issues are important concerns for individuals ageing with HIV in the UK [7,462]. The HIV and Later Life Study (HALL) qualitatively explored the lived experience of 123 participants ageing with HIV, with their findings illustrating many of the psychosocial factors at play. Stigma was widely felt, and different stressors were seen for different groups. Those of Black African origin born abroad reported difficulties regarding separation from families, and the stigma and uncertainty attached to being an immigrant or asylum seeker. Those with longer duration of HIV felt the loss of friends and loved ones early in the epidemic, expressing loneliness as well as survivor guilt. White heterosexuals felt particularly isolated and in the minority with less knowledge of HIV, fewer support resources and higher vulnerability to loss with disclosure amongst this demographic. Lastly, they feared stigma may worsen with age as peers were more likely to retain the negative stereotypes around HIV acquisition such poor judgement, engagement in risky behaviours, and irresponsibility [462].

Frailty itself has been viewed as a stressor or crisis, which one must navigate as they transition from robust to higher frailty states. How well one deals with these stresses depends on an individual's psychological and social resources [463].

Frailty versus successful ageing

Frailty, as described represents a negative ageing trajectory that puts the individual at risk of adverse outcomes. However, we have clearly demonstrated that a large proportion of the cohort exhibit no frailty traits and are therefore robust. This suggests that individuals exist on a spectrum of ageing with a proportion ageing more successfully than the population norm or usual ageing. Successful ageing (SA) can simplistically be referred to as retaining physical, mental and social well-being in older age and has been described to represent the opposite end of a continuum to pathological ageing [464], which some have suggested could equate to frailty [465]. Though frailty and SA are thought to be best represented as multidimensional entities they both lack consensus definitions; frailty has broadly focussed on loss or deficits often restricted to biomedical characteristics whereas SA focusses on positive states and promoting strengths

across health and particularly psychosocial functioning, whereby one could still exhibit SA in the presence of chronic illness such as HIV [103,465–467]. As such, much of the literature surrounding positive ageing traits are framed around SA and negative traits around frailty.

Well-being and resilience

Psychological well-being is dynamic and multifaceted and has been conceptualised by Ryff as having six domains: self-acceptance, an awareness of one's actions, motivations, and feelings; positive relations with others; autonomy, an ability to maintain independence; environmental mastery, an ability to shape environments to achieve personal goals; purpose in life, goal-setting to drive direction; and personal growth, realising one's potential [207]. Multiple factors influence well-being including health status, social class, emotional traits and social support. Maintenance of well-being relies on one's ability to be resilient, which may be defined as a preparedness for and the successful adaptation to negative life events, through the development and use of effective coping strategies [468–471].

Coping may be problem focussed (active), where one attempts to overcome the root cause of the stress event or emotion focused (passive), where one regulates the emotional response to that event. This was examined in a study of 305 Spanish adults (mean age 49.1) where problem-focused coping positively predicted resilience which in turn predicted well-being. However, emotion-focused coping was negatively associated with well-being, as these strategies are more often employed when a problem cannot be solved. Therefore, focus is placed on reducing emotional impact and 'living with it', some of which may be maladaptive resulting in low mood and anxiety [468].

Through interviews with PLWH aged over 50 regarding the challenges of ageing in the context of HIV, Emlet et al. identified seven themes or traits that were related to resilience including: self-acceptance; optimism; will to live, including purpose in life; generativity; self-management; relational living and independence. These traits map well to those thought to be central to psychological well-being [472].

We have discussed that throughout our life-course we are confronted with stress events which may be acute such as a fracture; longer-term such as negative early life experiences, or chronic such as disability and comorbidity including HIV. Resilience allows one to minimise the negative effect of these physical, psychological and social stressors with aim of maintaining health and function. We have introduced psychological resilience and we will discuss the role of social vulnerability, which may suggest that social resilience also exists. Whitson et al. performed a systematic review of physical resilience which they describe as the ability to recover from and/or adjust to age-related diseases or losses, which is influenced by psychosocial factors, genetics, physiological reserve, life experiences and the environment in which one lives. Those with physical resilience may age more successfully and potentially remain robust compared to less resilient individuals who may be at a higher risk of frailty [473]. However, there is no screening tool for physical resilience and this has not been examined directly but resilient traits, across physical, psychological and social domains may be protective against frailty.

Psychological factors and frailty

Psychological well-being may be a potential resource for positive ageing with higher psychological well-being suggested to be a protective factor for frailty. In the English Longitudinal Study of Ageing (ELSA) of 2557 older adults Gale et al. demonstrated that a standard deviation increase in well-being score was associated with a 38% reduction in relative risk of incident frailty (RR 0.62; 95% CI 0.52-0.74) and 21% for prefrailty (RR 0.79; 95% CI 0.71-0.89); with a linear relationship between increasing well-being and decreasing likelihood of prefrailty and frailty ($p<0.001$ trend) [474]. Aspects of well-being have also been associated with frailty with positive affect associated with a reduced incidence of frailty at seven years in a study of 1558 community-dwelling Mexican Americans (mean age 71.9) [475], and at two years in a study of 954 women enrolled to the Caregiver Study of Osteoporotic Fractures, which was independent of depression [476]. Additionally, lower life satisfaction has been associated with higher frailty states in independent and cognitively intact older adults over 80, with frail and prefrail individuals 6- and 2-times more likely to have poor life satisfaction [477].

Frailty has also been associated with poorer psychological well-being, including psychological distress [478]. In the Canadian Study of Aging and Health lower well-being was related to older age, lower education, greater frailty, poorer mental health and lower cognition. Here, increasing frailty was associated with lower well-being, with an additional frailty deficit on the FI associated with a 0.29 worsening on the Ryff well-being score (ß=0.29, 95% CI 0.22-0.36) [228]. This is supported by the Italian 3-year Act on Ageing longitudinal study where phenotypic frailty was significantly associated with all measured psychosocial factors (depression, loneliness, social isolation), which worsened as frailty increased [447]. Those with frailty and negative psychosocial factors were at greatest risk of ADL disability [447]. Lastly, a study of hospital inpatients showed that those with frailty were more likely to have higher symptoms of anxiety and depression, poorer well-being, lower sense of control and require more assistance from others. There was also an interaction between negative psychosocial factors and frailty, as those with both were more likely to encounter adverse outcomes (mortality, institutionalisation) than those without [479]. This modifying effect of psychosocial factors on adverse outcomes in frail individuals is not universal however as this was not observed in the Longitudinal Aging Study of Amsterdam [480].

Psychological well-being is related to known adverse outcomes of frailty with a meta-analysis demonstrating higher psychological well-being to be associated with lower mortality in those with (HR 0.98; 95% CI 0.95-1.00, p=0.03) and without illness (HR 0.82; 95% CI 0.76-0.89, p<0.001). Markers of both positive affect, including emotional well-being, positive mood, happiness and vigour, and positive emotional traits of life satisfaction, hopefulness, optimism and sense of humour were protective against mortality [481]. Poorer well-being and social interaction have also been associated with transfer to institutional care [479] and higher mastery and self-efficacy associated with lower odds of functional decline [480].

Psychological factors and HIV

Heckman et al. hypothesised that older PLWH may express elevated levels of psychological distress and coping difficulties, but in their study of 83 participants they showed low levels of psychological symptoms suggesting good

psychological adjustment overall. However, higher levels of HIV-related symptom burden, less social support, and barriers to healthcare predicted higher psychological distress [459]. A further study examined resilience in 151 middle aged PLWH showing it to be at least moderately high in 43% and very low in 19.2%. Higher resilience in multivariable analysis was associated with a greater sense of self, good perception of social relationships, using positive reframing to aid coping and better emotional status [482].

Negative psychological traits were seen in the Research on Older Adults with HIV (ROAH) study of 904 older adults in New York, USA. Here HIV-related stigma was high and associated with loneliness, depression, and decreased overall well-being [461]. Additionally, men in this study reported lower levels of acceptance, environmental mastery, purpose in life (PIL) and difficulty forming positive relationships [461]. Lastly, in the UK-based ASTRA study of 3258 PLWH, they demonstrated a lower prevalence of depression and anxiety in older compared to younger individuals. However, they found that longer duration of HIV was associated with both poorer physical and psychological health suggesting that well-being may be more closely related to duration of HIV infection rather than chronological age [259]. This may be due to the cumulative stress of more years lived with chronic disease as well as issues surrounding receiving an HIV diagnosis earlier in the epidemic where treatment efficacy and prognosis was poorer, stigma prevalent and social networks strained by loss

Social support and frailty

We all exist within social networks; the make-up of which varies between individuals though support can come from family, friends, neighbours, support groups, the wider community, and formal support structures (carers, advocates etc.). Social support is usually multi-dimensional with several sources providing aspects of physical and/or emotional support; though within social networks there may be issues of access, availability, belonging and connectedness. Therefore, the support we draw upon can represent social reserve, which if effective can boost resilience, coping and have positive effects on physical health and psychological well-being. Where lacking, inaccessible or ineffective it may leave the individual socially vulnerable.

There are many aspects to social vulnerability, such as inadequate support for physical or emotional needs; as well as social isolation or physical separation from other people, and loneliness where there is a disparity between actual and desired social contact. Though these may be related they are not synonymous [483]. Social vulnerability is dynamic and may increase with ageing where loss of individuals can gradually weaken, and health and functional problems reduce one's ability to engage with their social network. Additionally, social vulnerability may worsen physical, psychological and functional problems, and low social reserve has been shown to predict poorer self-perceived health, cognitive decline, ADL disability, falls risk, and frailty [206,484]. Further, social isolation predicts medical comorbidities in older adults [483] and emergency hospitalisation and mortality in those with and without HIV [226].

In the Canadian National Population Health Survey (N=2740, mean age 73.4) increasing frailty by frailty index score was associated with decreased social engagement, and higher scores on a social vulnerability index (comprising living situation, social support, engagement, relations with others, neighbourhood socioeconomic status, self-esteem and sense of control). This was associated with an increased risk of mortality at 10 years, increasing by 5% for every additional social deficit [484]. The effect of social support on frailty in relation to social network size, instrumental support, emotional support and loneliness was examined in the Longitudinal Aging Study of Amsterdam. Here increasing frailty state at baseline was associated with smaller social network size and increased loneliness, but not level of support [485]. At 3-year follow-up in their fully adjusted model frailty was not associated with any change in social network size but was significantly associated with worsening loneliness [485]. Additionally, a lack of social participation has been associated with a worsening of frailty over a two-years in a large study of adults aged ≥55 across ten European countries [486]; with good social support associated with slower increases in frailty seen elsewhere [487]. However, others have shown no association between social capital and frailty [488].

Hoogendijk et al. demonstrated longitudinally in frail older adults that though social network size did not shrink, their relationship with them altered with reduced interaction or reduced fulfilment of needs. This reduction in social

functioning but not size prompted the authors to suggest that having a small social network may increase one's risk of developing frailty, which should be examined in prospective longitudinal studies [485].

Social support and HIV

For older HIV-positive individuals there may be a number of barriers to adequate social support including a lack of availability due to older parents, fewer children and loss of partners/close contacts to HIV/AIDS; financial disadvantage; fear of HIV disclosure due to fears of stigmatization or loss of privacy; ignorance around HIV, especially acquisition and transmission risk; and self-reliance, maintaining independence and avoiding becoming burdensome [102,225,489]. Social isolation and loneliness are also common in this group and they may be at risk of social vulnerability due to smaller, fragile social networks providing inadequate social support [7,490,491].

Diverse groups of PLWH may rely on very different social networks. Emlet et al. examined social isolation in HIV-positive Americans demonstrating no difference in social support by age but older men and those of non-white ethnicity had fewer social contacts. Those identifying as homo- or bisexual received more social support from friends than family contacts [225]. Shippy et al. support this finding where MSMs are more likely to rely on friend and peer based social support [492]. Additionally, a cross-sectional study of 160 older HIV-positive adults in New York posed hypothetical situations to which 33% would first call on help from friends, 23% family, 14% formal support services, with 17% relying on themselves and 7% unsure who they would ask [102].

Social isolation in the VACS cohort was significantly higher in those with HIV compared to those without, which increased with age [226]. Shippy et al. found that of 160 older adults with HIV, 36% and 25% described only some or no access to instrumental and emotional support respectively [102]. This is echoed by Scrimshaw et al. in American older PLWH where 42% reported inadequate emotional and 27% inadequate practical support, which was more likely in those with a longer duration of HIV and/or AIDS diagnosis [489].

Therefore, many PLWH particularly if older do not rely on traditional support systems such as family, prompting concern over a future reliance on formal support systems including institutional care; with over 75% of participants in a UK study expressing concern over access to and desire for information about future support and social care, with the majority preferring this to come from HIV organisations [7]. However, where social support is adequate it has been shown to decrease distress and increase well-being, at least in HIV-positive MSMs where the effect was significantly stronger in older compared to younger men [493].

Health-related Quality of Life (HRQoL) and HIV

The shift to chronic disease status of HIV has increased focus on wider reaching effects including its impact on an individual's quality of life. HRQoL is a multidimensional construct that includes functioning across physical, emotional, cognitive and social domains. Well-being and positive psychosocial resources may help preserve one's QoL even in the face of medical and functional problems.

HIV may challenge HRQoL as seen in work by Miners et al. where it was compared in two large cross-sectional populations, using the ASTRA study of 3258 PLWH and the Health Survey for England of 8503 as a (presumed) HIV-negative control group. PLWH scored significantly lower on all domains of the Euroqol questionnaire (EQ-5D-3L) than those without HIV. This persisted across all CD4, VL and cART groupings, including those suppressed on effective cART, suggesting that HIV has wide ranging health implications, even in the face of good HIV control [494].

Many different tools have been used to measure HRQoL in PLWH [495]. Though this makes direct comparisons difficult, studies have shown good levels of HRQoL. A Swiss study using the WHO-QOL-HIV brief tool in 72 older adults with well-treated HIV (mean age 56.9; 75% male) found HRQoL to be very good in 66% [490]. Balderson et al. showed reasonably well-preserved HRQoL in 452 older HIV-positive Americans (mean age 55.8, 72% male, majority African-American) with high levels of comorbidity and cART non-adherence with highest scores obtained for social functioning, followed by mental health and then physical functioning using the Short Form-36 tool [274]. Lastly, in the HALL study over half

(56%) reported good/very good QoL with only 10% rated poor. However, on interviewing QoL was described as a variable phenomenon and goal that one must work hard at to achieve through knowledge, adherence, mobilising support, optimism, and decentralising HIV in their lives [462].

Predictive and protective factors for HRQoL represent both intra- and interpersonal resources and are consistent across the studies. Lower HRQoL is associated with female gender, non-white ethnicity, longer duration of HIV [494]; mental and physical health problems; increased social support needs; financial disadvantage, and victimisation, rejection or stigma [462,490,496–498].

Two cross-sectional studies of HRQoL (SF-12) in PLWH in France conducted at two time-points of 2002 (VESPA) and 2011 (VESPA2) were compared. Using group statistics, they showed a decrease in physical HRQoL from 49.6 to 47.5 ($p<0.001$) but an increase in mental HRQoL of 44.3 from 42.3 ($p<0.001$) between the time periods; observing that HIV-factors became less influential at the later time-point [498]. Supporting this is a study examining HRQoL in 226 older American gay and bisexual men (mean age 63.0) where HIV alone did not predict HRQoL, with greater importance attached to comorbidities and functional limitations, which prompted authors to suggest that long-term survival may diminish the relationship between HIV and QoL [497].

Aims and Hypotheses:

The aim of the first section of this chapter is to describe markers of psychosocial functioning, focussing on social networks, purpose in life, grit and quality of life within the cohort and by frailty status. We selected two psychological resources to study, namely grit and purpose in life. Grit is a positive, non-cognitive trait which encourages long-term goal setting accompanied by a strong motivation to achieve them, through perseverance, and tackling challenges that may disrupt goal attainment. Grit has been linked to hardiness and resilience and potentially increases across the life-span [203]. Purpose in life (PIL) has been proposed as a key dimension of psychological well-being and describes the sense that one's life has meaning and direction, and as such greater PIL has been associated with positive psychological and physical outcomes [207,227]. Social network size and support were assessed using the Lubben Social Network Scale (short-form).

In line with the aims of this chapter we set the following hypotheses.

Hypothesis 1: PIL and psychological grit will be lower in those with frailty compared to non-frail individuals, with both traits worsening as frailty increases

Hypothesis 2: Frail individuals will have smaller social networks and exhibit higher levels of social isolation, with social support worsening as frailty increases. Additionally, these social networks are more likely to be friend rather than family orientated.

Hypothesis 3: All the above psychosocial traits will diminish as level of frailty increases with prefrail individuals representing an intermediate group, who based on their FFP score can be identified as being closer to robust or frail states in terms of psychosocial status.

Hypothesis 4: Higher states of frailty will be associated with poorer HRQoL.

6.1.2 Methods

Overview:

All 253 participants were asked to complete the main study questionnaire in which all psychosocial questionnaires were embedded. The names of the individual questionnaires or concepts tested were not explicitly included within the questionnaire to minimise reporting bias. The full details of each of the questionnaires used and constructs tested are described in detail in chapter three but are summarised below.

Lubben social network scale-6 (LSNS-6) [205,206]

The LSNS-6 is an abbreviated version of the original LSNS and comprises two identical sets of three questions, referring separately to family and then friendship ties. These questions, given here for family members, are: How many relatives do you see or hear from at least once a month? How many relatives do you feel close to such that you could call on them for help? How many relatives do you feel at ease with that you can talk about private matters?

Participants are asked to respond with choices of none, one, two, three to four, five to eight or nine or more people for each question. These responses correspond to respective scores from 0-5 that are directly summed to provide an

overall scale score from 0-30. Social isolation is indicated by scores <12 overall and <6 on each of the three item subscales scores indicating either marginal family or friendship ties [206].

Additionally, to assess availability of social support participants were asked the single question “When you need help, can you count on someone who is willing and able to meet your needs?” with “always”, “sometimes” or “never” presented as response options.

Purpose in life scale (PIL) [207,227]

We utilised the 10-item PIL scale derived from Ryff’s scales of psychological well-being [207], operationalised in work by Barnes [229] and Boyle [227,230]. It comprises 10 statement questions, which were rated in terms of agreement, on a scale of 1-5, which is reversed for negatively worded statements. The scores for each statement were totalled, with the mean of the total taken as the score. Higher scores indicated greater PIL [230].

Short grit scale (Grit-S) [203,204]

We utilised the Grit-S, a valid and reliable 8-item scale, where participants were asked to rate eight statements on a 5-point scale. Positively worded statements were scored from ‘very much like me’=5 to ‘not like me at all’=1, which was reverse scored for negative statements. Statement scores are totalled and divided by 8 to provide a mean, ranging from a maximum score of 5 (extremely gritty) to a lowest score of 1 (not at all gritty) [204]

Short Form-12 (SF-12) assessment of quality of life [200]

To assess health-related quality of life (HRQoL) we utilised version 2 of the Short-Form 12-Item Health Survey (SF-12), a validated measure of HRQoL that provides insight into the participant’s current perceived physical and mental health status. The SF-12 comprises eight domains of general health, physical functioning, pain, role limitation due to physical health, role limitation due to emotional problems, mental health, vitality and social functioning. Additionally, the domains were summarised into the Physical Health Component Summary (PCS) and the Mental Health Component Summary (MCS). Each of the eight

domains and the component scores range from 0-100, with higher scores representing greater HRQoL [216].

Statistical considerations

All variables were assessed for normality with descriptive statistics presented as frequencies with corresponding percentages for categorical data. Continuous data is presented with mean and standard deviation for normally distributed data and median and interquartile range if skewed.

Core analyses compared frail to non-frail (pre-frail and robust participants) individuals using chi-squared tests (categorical data), unpaired two-sided t-tests (normally distributed continuous data) and Mann-Whitney U test (non-normally continuous data) where appropriate.

Predictors of frailty were explored across two frailty groups (non-frail, frail), and across four groups by dividing the prefrail group into those scoring one on the FP, representing those closer to the robust group and those scoring a two, who are those closer to the frail group, with the groups described as robust, pre-frail A, pre-frail B and frail. Across group analyses were conducted using chi-squared tests (categorical data), one-way ANOVA (normally distributed continuous data) and Kruskal-Wallis test (non-normally continuous data) where appropriate and where relevant assumptions have been met with or without data transformation (squaring or raw values).

Where ANOVA results were significant, pairwise examinations were made using the Tukey post hoc test. Pairwise ranks-based comparisons were used following Kruskal-Wallis tests. As such, Bonferroni correction was applied to account for multiple comparisons made when assessing the four levels of frailty of robust, prefrail A, prefrail B and frail, representing six pairings. Here, to preserve the type I error rate, statistical significance was attained if $p<0.008$.

Associations with frailty were assessed using univariate and multivariable logistic regression to obtain OR for any association, presented with its 95% confidence interval and p-value. The multivariable model created in chapter 4 was used unless otherwise stated.

For tests, apart from any post-hoc analyses, statistical significance was taken at the 95% level with p-values <0.05. All analyses were performed in Stata version 13.

6.1.3 Results

All 253 participants completed the study questionnaire, with full data for the LSNS-6, PIL scale and SF-12 and one participant with missing data on the Grit Scale. Core analyses used the predefined frailty groups of frail (19%) and non-frail (81%). To examine the trends across frailty categories we divided the prefrail group into those scoring 1 (prefrail A), which represents those closer to robust state and those scoring 2 (prefrail B) representing those closer to the frail state. This meant 94 (37.1%) were robust, 58 (22.9%) prefrail A, 53 (21.0%) prefrail B and 48 (19.0%) frail.

Psychosocial traits: frail vs non-frail

Table 6.1 shows the scores for PIL, grit and social support for the full cohort and divided by frail and non-frail groups. Scores for both PIL, $z=5.55$, $p<0.001$ and grit, $t(250)=3.54$, $p<0.001$ were significantly lower in those with frailty compared to those without. Frail individuals reported significantly lower social support overall, $t(251)=3.16$, $p=0.002$ and with respect to both family members, $t(251)=2.45$, $p=0.015$ and friends and neighbours, $t(251)=2.45$, $p=0.015$. Regarding social networks, higher mean scores were reported for friend-based social contacts and support compared to family based (7.4 vs. 5.1). Social isolation (LSNS-6 scores<12) was common in the cohort affecting 46.3%, which was significantly higher amongst those with frailty, $X^2(252,N=253)=7.97$, $p=0.005$. Over half (53.8%) were isolated from family members, with weak evidence that this was related to frailty $X^2(252,N=253)=3.97$, $p=0.046$. However only a quarter were isolated from friend contacts, which was not significantly different based on frailty status, $X^2(252,N=253)=2.02$, $p=0.155$. With regard to available and willing help in the time of need, frail individuals were less likely to always have this need met, however this difference did not reach statistical significance, $X^2(252,N=253)=3.98$, $p=0.137$.

Table 6.1: Psychological traits and social support across the full cohort and by non-frail and frail groups

Variable	Full cohort N=253 (%)	Non-Frail N=205 (%)	Frail N=48 (%)	Test Statistic	*p* [a]
Purpose in life [b]	3.6 (3.0-4.1)	3.8 (3.2-4.3)	2.9 (2.3.5-3.4)	z=5.55	**<0.001**
Grit [c] (N=252)	3.61 (0.65)	3.68 (0.62)	3.31 (0.74)	t=3.54	**<0.001**
Social support [c]	12.6 (5.3)	13.1 (5.0)	10.5 (8.8)	t=3.16	**0.002**
Family support [c]	5.1 (3.4)	5.4 (3.3)	4.1 (3.9)	t=2.45	**0.015**
Friend support [c]	7.4 (3.3)	7.7 (3.3)	6.4 (5.5)	t=2.45	**0.015**
Socially isolated	107 (46.3)	78 (38.1)	29 (60.4)	X^2=7.97	**0.005**
Family isolation	136 (53.8)	104 (50.7)	32 (66.7)	X^2 =3.97	**0.046**
Friend isolation	64 (25.3)	48 (23.4)	16 (33.3)	X^2 =2.02	0.155
Available help					
Always	138 (54.6)	118 (57.6)	20 (41.7)	X^2 =3.98	0.137
Sometimes	102 (40.3)	77 (37.6)	25 (52.1)		
Never	13 (5.1)	10 (4.9)	3 (6.3)		

[a] p-value based on X^2 test unless stated.
[b] median (IQR); p-value based on MWU test providing z-statistic.
[c] mean (sd); p-value based on two-way t-test providing a t-statistic

Psychological traits (four frailty groups):

Violation of assumptions called for squared transformation of both grit and PIL data before undertaking one-way ANOVA; the results of which are shown in Table 6.2. The mean Grit score decreased with higher frailty state which was statistically significant using one-way ANOVA ($F(3,248)=7.59$, $p<0.001$), meaning that less frail individuals were grittier. We applied a post-hoc Tukey HSD test, which showed no statistical difference between those individuals classed as prefrail A compared to robust (-0.03, p=0.986) or in those with frailty compared to prefrail B (-0.58, p=0.918). After Bonferroni adjustment, the difference between prefrailty B and A was no longer significant (-2.30, p=0.038). All other pairings were significant, prefrail B compared to robust (-2.56, p=0.006), frail compared to robust (-3.14, p=0.001), frail compared to prefrail A (-2.88, p=0.007). Therefore, those in the robust and prefrail A groups were more similar, and significantly different to the prefrail B and frail groups that were more closely related.

The mean PIL score decreased with higher frailty state which was statistically significant using one-way ANOVA (F(3,249)=21.59, p<0.001). A post-hoc Tukey test showed no significant difference between prefrail A and robust; prefrail B and prefrail A; and frail and prefrail B pairings after applying Bonferroni correction. The three other pairwise comparisons revealed significant differences in mean PIL scores, which were lower in each of the higher frailty conditions within the pairing including frail compared to robust (-6.72, p<0.001), frail compared to prefrail A (-5.04, p<0.001) and prefrail B compared to robust (-3.96, p<0.001. This supports other findings that prefrail A is closer to robust state and prefrail B to frail, though not significantly different from each other. PIL may be protective in transitioning to higher frailty scores.

Table 6.2: The distribution of grit and purpose in life scores across the four predefined frailty groups.

Variable Mean (sd)	Robust N=94	Pre-frail A N=58	Pre-Frail B N=53	Frail N=48	F	*p* [a]
Grit[2]	14.64 (3.95)	14.38 (4.89)	12.08 (4.70)	11.50 (4.82)	7.59	**<0.001**
Grit mean	3.83	3.79	3.48	3.39	-	-
Purpose[2]	15.69 (4.57)	14.01 (5.33)	11.73 (5.83)	8.97 (4.14)	21.59	**<0.001**
Purpose mean	3.96	3.74	3.42	2.99		

[a] p-value based on one-way ANOVA with squared transformation of raw data

Social support (four groups):

Level of social support as measured by the LSNS-6 was associated with frailty. It decreased with increasing frailty status as shown in Table 6.3. The group difference was statistically significant using one-way ANOVA (F(3,249)=7.80, p<0.001). This same significant decrease in social network size and support was seen in separate one-way ANOVA conducted for family (F(3,249)=4.69, p=0.003) and friends components of the LSNS-6 (F(3,249)=5.13, p=0.001).

Post-hoc pairwise analysis (Tukey) on the full support score showed no statistically significant difference between adjacent pairings: frail-prefrail B (-0.65, p=0.947); prefrail B-prefrail A (-2.25, p=0.093); prefrail A-robust (-0.88, p=0.727)

or between frail-prefrail A (-2.81, p=0.026) after considering the Bonferroni adjustment. Overall support was significantly lower when comparing frail to robust (-3.69, p<0.001) and prefrail B-robust (-3.13, p=0.002) indicating lower social support in those with and at greatest risk of frailty.

Regarding family, in post hoc analysis the only significant differences were seen between frail and prefrail A (-1.82, p=0.031), and frail to robust (-1.67, p=0.028). No other pairwise tests were significant: frail-prefrail B (-0.22, p=0.988), prefrail B-prefrail A (-1.60, p=0.063), prefrail A-robust (0.14, p=0.994) and prefrail B-robust (-1.45, p=0.061). Frail individuals had a significantly lower mean score on the friendship aspect of the LSNS-6 when compared to robust participants (-2.02, p=0.003). There were no other significant pairwise differences in relation to friend or family support. Figure 6.1 summaries the distribution of scores for PIL, grit and social network support.

Table 6.3: The distribution of social support scores across the four predefined frailty groups.

Variable	**Robust**	**Pre-frail A**	**Pre-Frail B**	**Frail**	**F**	***p*** [a]
Mean (sd)	**N=94**	**N=58**	**N=53**	**N=48**		
Total support	14.19 (4.68)	13.31 (5.15)	11.06 (4.79)	10.5 (6.01)	7.80	**<0.001**
Family Support	5.73 (3.41)	5.89 (3.10)	4.28 (3.08)	4.06 (3.86)	4.69	**0.003**
Friendship support	8.46 (3.07)	7.43 (3.47)	6.77 (3.21)	6.44 (3.34)	5.13	**0.001**

[a] p-value based on one-way ANOVA

We examined whether social isolation varied by frailty category, with results and accompanying Chi-squared values shown in Table 6.4. The proportion of those considered socially isolated on the LSNS-6 was significantly different across the frailty groups with around 30% of robust and prefrail A individuals being isolated, which increased to around 60% in the prefrail B and frail groups, $X^2(252,N=253)=7.97$, p=0.005). This lends weight to our hypothesis that prefrail A group are more like robust individuals and the prefrail B group are more like frail individuals. A similar pattern is seen in terms of family isolation and to a lesser

extent for isolation within friendship networks. Pairwise relationships have not been explored further in terms of social isolation.

Table 6.4: Levels of total, family and friend isolation by frailty category.

Variable N (%)	Robust N=94	Pre-frail A N=58	Pre-Frail B N=53	Frail N=48	X^2	*p* [a]
Social isolation	30 (31.9)	27 (29.3)	31 (58.5)	29 (60.4)	20.31	**<0.001**
Family isolation	45 (47.9)	25 (43.1)	34 (64.2)	32 (66.7)	9.48	**0.024**
Friendship isolation	15 (16.0)	15 (25.9)	18 (34.0)	16 (33.3)	8.10	**0.044**

[a] p-value based on chi-squared test

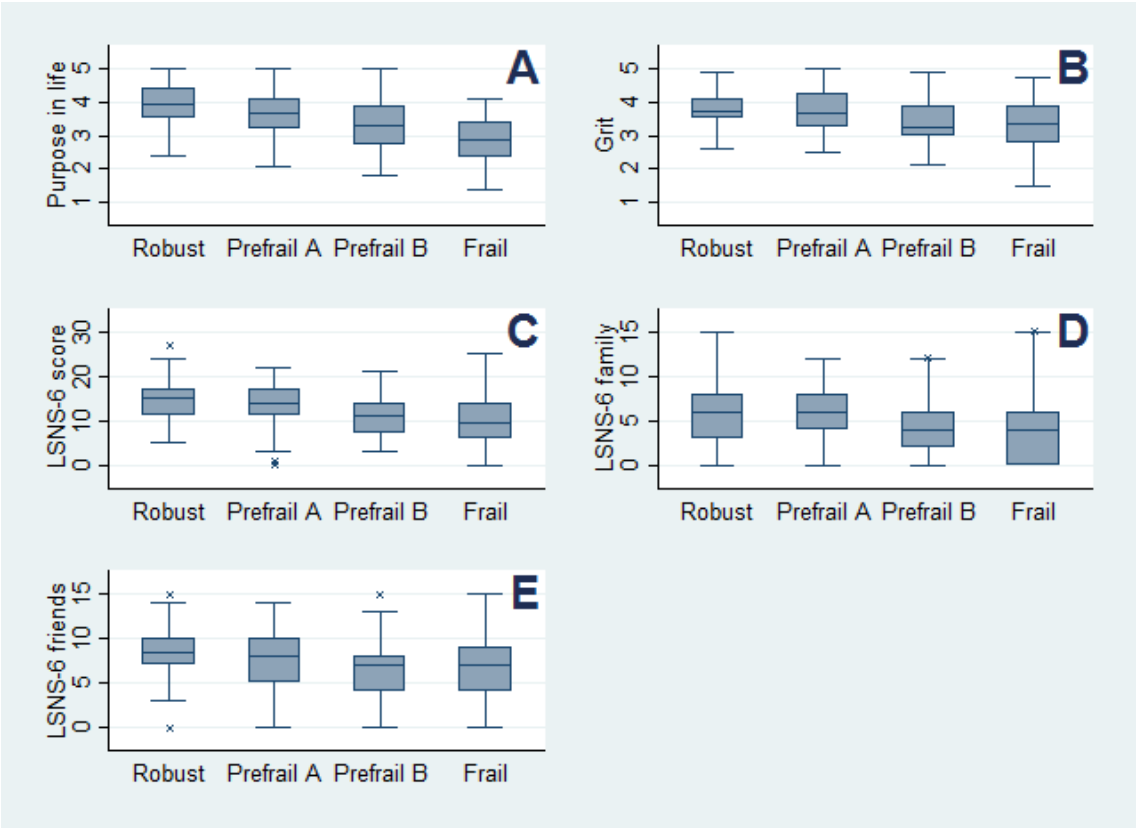


Figure 6.1: Distribution of median scores for psychosocial traits across four frailty groups. Depicting change by frailty status for A) Purpose in life B) Grit C) Total social support D) Family support and E) Friendship support

Health-related quality of life

Table 6.5 demonstrates the scores for each of the eight domains comprising the SF-12 HRQoL tool and the two composite scores that reflect physical (PCS) and mental (MCS) HRQoL respectively, with higher scores representing greater HRQoL related to that domain. In the full cohort, the highest median scores were seen for physical functioning (75), social functioning (75), pain (75) and emotional role limitation (75) and lowest for energy (50) and general health (60). Frail and non-frail groups were then compared revealing significantly lower HRQoL on all eight domains for those with frailty (all $p<0.001$). Frail participants reported highest HRQoL in terms of mental health (50) and emotional role limitation (50) and poor HRQoL in the domains related to general health, symptoms (pain, energy), and physical functioning including socially and fulfilling physical roles. The PCS and MCS are standardised to a have a mean score of 50 using a US population norm, though scores were skewed in our population. However, the full cohort had marginally lower than average HRQoL on both the PCS (48.2) and MCS (48.5). When compared, non-frail individuals had about average HRQoL but this was significantly lower for frail individuals on both physical (32.4) and mental (41.9) scores.

We examined how HRQoL varied across the four frailty categories as outlined earlier with results presented in Figure 6.2. All the quality of life parameters decreased as frailty state increased and Kruskal-Wallis tests demonstrated significant differences in the median scores across the four frailty groups for each of the eight HRQoL domains and the PCS and MCS values (all $p<0.001$). These data are not presented further.

Table 6.5: Median values for the quality of life domains and corresponding physical and mental component scores for frail and non-frail individuals.

Variable	Full cohort N=253 (%)	Non-Frail N=205 (%)	Frail N=48 (%)	Z-score	*p* [a]
General health	60 (25-85)	60 (60-85)	25 (25-42.5)	6.78	**<0.001**
Mental health	62.5 (50-75)	75 (50-87.5)	50 (37.5-62.5)	4.34	**<0.001**
Physical functioning	75 (50-100)	75 (50-100)	25 (0-50)	8.96	**<0.001**
Social functioning	75 (50-100)	75 (50-100)	25 (25-50)	5.98	**<0.001**
Pain	75 (50-100)	75 (50-100)	25 (25-62.5)	6.49	**<0.001**
Energy/vitality[b]	50 (25-75)	50 (50-75)	25 (25-25)	6.84	**<0.001**
Role limitation-physical	62.5 (50-100)	75 (50-100)	25 (12.5-50)	8.57	**<0.001**
Role limitation-emotional	75 (50-100)	87.5 (62.5-100)	50 (37.5-75)	5.70	**<0.001**
Physical HRQoL (PCS)	48.2 (37.1-55.7)	51.3 (42.6-56.9)	32.4 (27.8-37.8)	8.62	**<0.001**
Mental HRQoL (MCS)	48.5 (40.3-55.6)	50.5 (43.2-56.2)	41.9 (35.7-47.8)	3.95	**<0.001**

[a] median (IQR); p-value based on MWU test unless stated

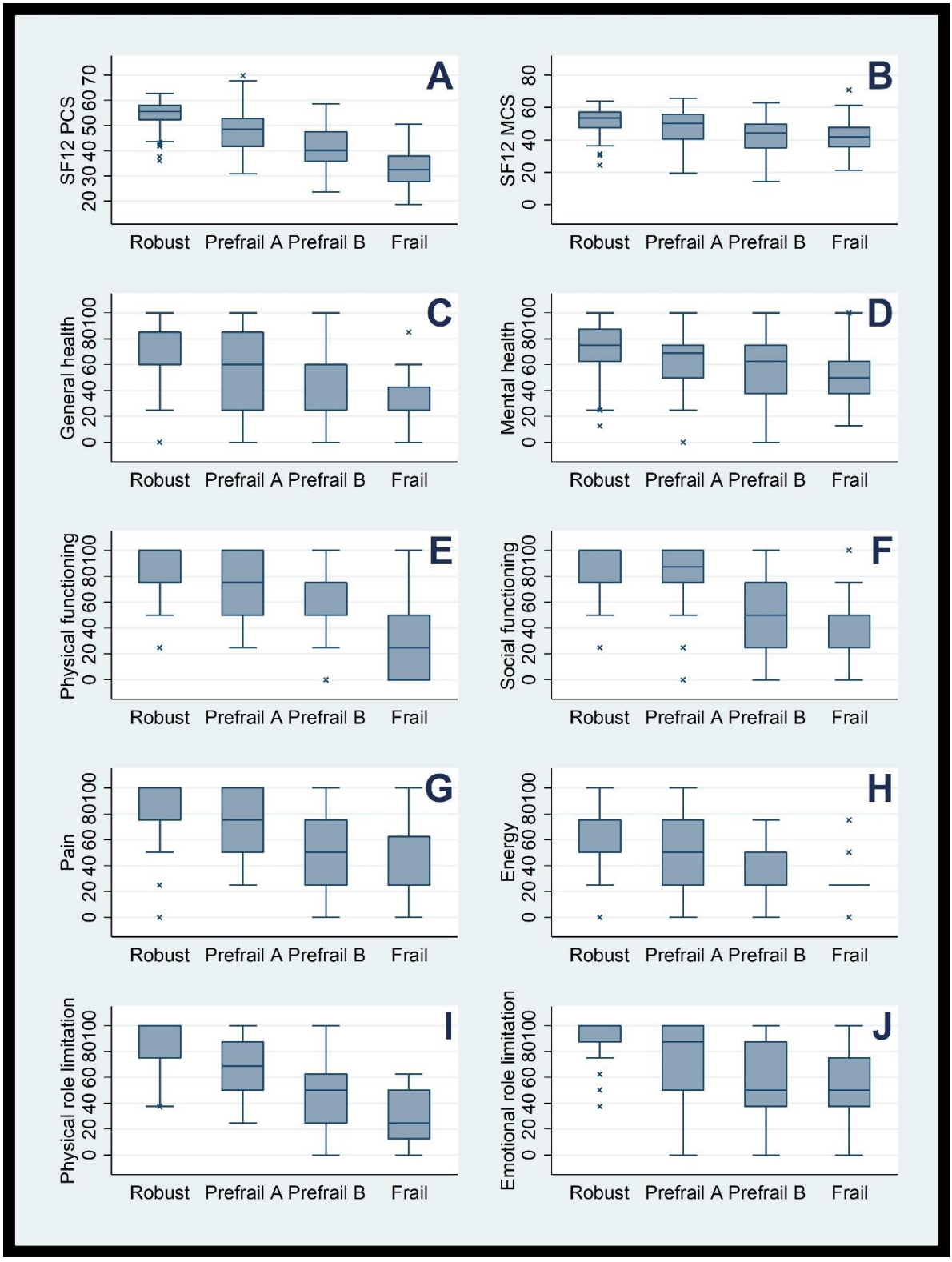


Figure 6.2: Boxplots of QOL domain scores across the four predefined frailty groups. Median (+IQR) shown for A) physical HRQoL (PCS) B) mental HRQoL (MCS) C) general health D) mental health E) physical functioning F) social functioning G) pain H) energy I) physical role limitation and J) emotional role limitation.

Associations between psychosocial factors and frailty

We used logistic regression to investigate the association between psychosocial resources and HRQoL domains and frailty as shown in Table 6.6. Higher levels of grit, PIL, social support and HRQoL across all domains were associated with significantly lower odds of frailty in univariate analysis. Though we had hypothesised a protective effect of higher PIL, grit and social support, in multivariable analysis controlling for age, sex, HADS score and number of comorbidities only a greater PIL retained borderline significance for the psychosocial resources, with a one-point increase in purpose of life score associated with a 7% reduction in likelihood of frailty (aOR 0.93; 95% CI 0.87-1.00, p=0.050). Social isolation was not related to frailty in either univariate or multivariable analyses (data not shown).

Having a greater sense of HRQoL in relation to one's general health, impact of bodily pain, energy levels, physical functioning and ability to perform roles despite any physical limitations were all protective for frailty with a one point increase in the respective domain scores associated with between a 3-6% reduction in the odds of frailty (p-values ≤0.001). These predominantly reflect the physical components of SF-12 and as such a higher physical HRQoL (PCS) was associated with a 16% decrease in the odds of frailty (aOR 0.84; 95% CI 0.79-0.89, p<0.001). Mental health, social and emotional functioning were not associated with frailty in adjusted analyses.

Table 6.6: Univariate and multivariate analysis of the role of psychosocial traits on likelihood of frailty compared to a non-frail reference group.

		Association with frailty		
Variable	**Crude OR (95% CI)**	**aOR [a]**	**95% CI**	**p-value**
Grit	0.42 (0.25-0.69)*	0.98	0.51-1.89	0.960
Purpose in life	0.88 (0.84-0.92)**	0.93	0.87-1.00	**0.050**
Social support	0.91 (0.85-0.97)*	0.94	0.87-1.02	0.143
Family support	0.89 (0.80-0.98)*	0.91	0.80-1.02	0.104
Friend support	0.89 (0.81-0.98)*	0.96	0.85-1.08	0.510
General health	0.96 (0.94-0.97)**	0.97	0.95-0.99	**0.001**
Mental health	0.97 (0.95-0.98)**	1.01	0.98-1.03	0.542
Physical functioning	0.94 (0.93-0.96)**	0.95	0.93-0.97	**<0.001**
Social functioning	0.97 (0.96-0.98)**	0.99	0.97-1.00	0.059
Pain	0.97 (0.96-0.98)**	0.97	0.96-0.99	**<0.001**
Energy/vitality	0.95 (0.93-0.97)**	0.96	0.94-0.98	**<0.001**
Role limitation-physical	0.94 (0.92-0.96)**	0.94	0.92-0.96	**<0.001**
Role limitation-emotional	0.97 (0.96-0.98)**	0.99	0.97-1.01	0.336
Physical HRQoL (PCS)	0.83 (0.79-0.88)**	0.84	0.79-0.89	**<0.001**
Mental HRQoL (MCS)	0.95 (0.92-0.98)*	1.05	0.99-1.11	0.088

[a] Adjusted for age, sex, HADS score and comorbidity count
* p<0.05; ** p<0.001

6.1.4 Discussion

As hypothesised, in this cohort being frail and higher frailty states were associated with lower self-reported purpose in life (PIL), psychological grit, social support and HRQoL. Social isolation was also seen to be higher in those with frailty but access to social support in time of need was not.

We have demonstrated that frail individuals were significantly less gritty and report lower PIL scores compared to those without frailty with both traits decreasing as frailty status increased, particularly PIL. Higher grit and greater PIL

were protective for frailty in univariate analysis but after controlling for age, sex, HADS score and number of comorbidities this protective effect was no longer significant for grit and of borderline significance for PIL (p=0.005), with most of the confounding effect on these traits mediated by higher symptoms of anxiety and depression on the HADS score.

The effect of PIL

PIL appeared to be the trait most associated with frailty in this cohort with higher ratings offering protection against likelihood of being frail and appearing to be important in distinguishing higher and lower risk in prefrail individuals. PIL describes the extent to which individuals feel their lives had meaning, purpose, and direction and is one of the pillars of psychological well-being proposed by Ryff [207,499]. These traits can be seen to belong to eudiamonic well-being, focusing on meaning and self-realisation including PIL, which can be compared to hedonic well-being that concerns seeking pleasure and avoiding pain and is therefore expressed by moods and feeling such as happiness, anger, sadness [499,500]. Measures of eudiamonic well-being have been used as an instrument to assess how individuals tackle the challenges and transitions occurring throughout the lifespan, particularly older age, with those with higher eudiamonic as opposed to hedonic well-being having broadly better outcomes [481,499,500].

There are conflicting views as to how both well-being and PIL change across life, though there appears to be a nadir in overall well-being around the mid-50s with improvements seen after this [500], though PIL is thought to decrease in later life [499]. Therefore, given the demographic of our cohort with just over half aged under 60, we may be capturing individuals at a chronologically low point in well-being.

Eudiamonic well-being and PIL have been investigated in the context of physical health and physiology to try and identify mechanism by which the two may interact. Higher PIL has been associated with decreased risk of disability [501,502], vascular disease [503,504] cognitive impairment [230,505], and mortality [227]. Higher PIL may influence biological pathways, including an association with lower inflammation [506] and allostatic load [507]. Allostatic load is the collective physiological burden experienced through mounting protective and corrective responses to stress events across multiple body systems, which may contribute

to biological frailty, suggesting that PIL may positively influence ageing physiology. Additionally, higher PIL was associated with a higher sense of self-control over health, which mediated some of the relationship between PIL and allostatic load potentially through those with better self-control being proactive in engagement with health [507]. Others support this relationship, with higher PIL associated with higher use of preventative health services, such as screening [508] and positive well-being related to favourable health behaviours, such as avoidance of smoking and taking regular exercise [481]. These findings, alongside the role of PIL in reducing the risk of depression and promoting positive coping strategies to health stressors in PLWH [509,510] may help to explain the relationship between PIL and frailty observed here. However, it should be noted that the protective role was only of borderline significance in this study and work by Andrew et al. showed no association between PIL and frailty, though this was based on two questions representing a PIL domain within a broader well-being tool, which did not have good discriminative ability [228]. Regardless, potential connections between PIL and known pathophysiological, behavioural (exercise) and affective (depression) mechanisms of frailty exist, promoting the role for further examination in longitudinal studies.

The effect of grit

Grit has been defined as perseverance and passion for long-term goals [203], and gritty individuals maintain interest in and sustain efforts towards achieving the targets they set for themselves despite failure, adversity or lack of positive feedback. Grit has been associated with higher attainment, particularly in education and employment and there is evidence to suggest grit increases with age [203,204]. It is assumed that if one is gritty then the trait will pervade multiple aspects of that person's life.

Grit incorporates motivation, perseverance, task orientated coping and goal pursuit which may contribute to overall psychological resilience. We demonstrated that those with frailty had lower gritty tendencies, with grit decreasing as frailty increased. However, it was no longer associated with frailty after controlling for age, sex, HADS and comorbidity. This is the first exploration of grit in relation to frailty to our knowledge and the finding that grittier individuals

are less likely to be frail is tenable within the construct of the trait. When faced with health challenges, including their HIV diagnosis, gritty individuals may not let health stressors stand in the way of long-term goals, one of which may be to maintain good health; as such grittier individuals may be more likely to undertake behavioural modifications such as engaging in physical activity, becoming knowledgeable about diagnoses and maintaining adherence to treatment regimes. They may also have prepared for and adapt constructively to the challenges of older age, whereas those without such resources may maladapt and risk more negative ageing outcomes. Certainly, adolescent grit has been shown to predict later life cognitive capacity with grittier individuals less likely to exhibit cognitive decline, which may be due to personal challenge and deliberate practice, such as cognitive training, as well as a capacity for delayed gratification where behavioural change is worth it if the ultimate outcome is good, such as stopping smoking to avoid vascular disease long term[511]. Alternatively, grit may enhance educational success, providing grittier individuals with the resources to seek knowledge, appraise risk, and access, engage with and maintain control over healthcare or through employment confer financial advantage, with both this and education shown to be protective for frailty [139,281,512,513]. However, we have not explored the relationship between grit, frailty and socioeconomic factors here.

The effect of social support

Level of social support was relatively low in this cohort with almost half (46%) meeting the criteria for social isolation, whereby individuals lack sufficient social contacts to provide a social support structure with in built redundancy. Social support as assessed by network size was lower in this study compared to a large population used to validate the LSNS-6 where total score ranged from 16.1-17.9 and social isolation from 11-20% depending on country studied, with family support higher than that provided by friends [206]; and compared to a study of older PLWH where mean total LSNS-6 score was 13.9 [514]. However, social isolation in a cohort of older adults with HIV in San Francisco was comparable to that seen in this study at 50.1%, which did not increase with age [491].

Social support was significantly lower in frail individuals in terms of total and family based support, but not support provided by friends. As hypothesised,

scores for friend based-support were higher than that reported for family, with only a quarter reporting social isolation with respect to friends compared to over half (54%) for family. Though friend support remained significantly lower for frail individuals, there was no difference in being socially isolated from friends. A reduced level of family support has been seen in PLWH [102,225,462], which may be secondary to many factors but compounded here due to the older age of the cohort where family contacts may not be available due to death of parents and siblings, and the higher proportion of MSMs in the cohort may mean they are less likely to have had children on whom they could rely. Families may be more geographically spread than friendship circles, which may be more likely to be retained locally. Therefore, this reduction in family support may be due to reduced availability rather than relationship strain, or unwillingness to ask for or provide support. Additionally this pattern may not be true globally, where in some countries and cultures family support structures may be traditionally stronger, such as India [515].

Social support decreased and in turn social isolation increased in totality and in relation to both family and friends as frailty state increased, and although higher social support was protective for frailty in univariate analysis this relationship did not persist after controlling for age, sex, mood symptoms and comorbidities. Additionally, it is important to note that although frail individuals were less likely to have help available when needed compared to those without frailty the difference was not significant. So, though social support may be lower, those with frailty had equal means of gaining practical help, but again we cannot comment on who would be called on to provide such support.

In line with our findings, a longitudinal study showed frailty to be associated with smaller social network size and loneliness but not social support, with size unchanged but loneliness increased at follow up, prompting authors to question whether smaller social networks may increase the risk of developing frailty [485]. Additionally, an American study of 102 older PLWH showed three constructs of social resources: social belonging, social support network size (using the LSNS-6) and social capital to be moderately correlated in bivariate analyses (ρ=0.36-0.44, all p-values<0.001), suggesting they represent related but not completely

overlapping concepts. Importantly they predicted different health outcomes with social belonging associated with medication adherence and life satisfaction, which was also related to social capital. However, social support networks were not associated with any health outcome in this study [514]. Both imply that social network size, which we have primarily measured, may not capture the nuances of the structure, nature or quality of one's social resources and how one interacts with their social network, including how formal support structures begin to feed in, which has been described as limitation of the LSNS-6 [514]. Additionally, though we could derive a marker of social isolation from the LSNS-6 we did not include any measure of loneliness, which appears to be associated with negative outcomes in PLWH and older adults, especially in the context of frailty.

Our findings do suggest a more complex relationship between social contacts and frailty, and we clearly cannot comment on the social dynamics of this cohort or social situation before the development of frailty. The fact that there appears to be a gradation in social support with a decrease with increasing frailty may add weight to Hoogendijk's argument that smaller social networks may be a risk factor for frailty; with Andrews et al. suggesting that a higher social reserve provided by a well-connected and supportive social situation may boost resilience and offset vulnerability to stressors [484,516]. Furthermore, increasing frailty has been associated with decreased social engagement so it is feasible that social circles and hence social reserve may shrink with increasing frailty due to an inability to interact with it secondary to factors such as illness, fatigue, and functional decline.

How social vulnerability may contribute to frailty risk is unclear however it has been suggested that remaining socially engaged may encourage physical activity, provide encounters that promote positive health behaviours, promote a sense of belonging, and provide opportunities for sharing concerns, seeking advice and receiving feedback, which can be a method of problem-based coping. Additionally, negative affect has been connected with frailty risk and social support has been associated with increased emotional support, decreased psychological distress, better mental health and increased well-being in those with and without HIV [206,493].

Though we have found lower social network size/support in frail individuals it was not associated with increased odds of frailty or conversely a protective effect. In keeping with this, others have argued against the inclusion of social functioning into frailty assessment tools, as it is felt to be distinct from frailty [517] and social components embedded within multidimensional frailty tools have not been shown to predict adverse outcomes [518]. The interaction between social support and frailty development, progression and outcomes does warrant further investigation however.

The role of prefrailty

Frailty is a dynamic process, but the trajectory in the main is to progress to higher frailty states as one ages [138], thus prefrail individuals represent those at the highest risk of transitioning to overt frailty. Gill et al. showed that those scoring on one criterion had the highest chance of reversion to robust status with those scoring on two criteria more likely to progress to frailty [138]. We therefore hypothesised that in terms of psychosocial factors there would be a separation of traits dividing those at risk (frail and prefrail B) and those not (robust and prefrail A), with more positive traits seen in this latter pairing. This was witnessed for grit and PIL, though in both situations the two prefrail groups were not significantly different from each other. Such a clear relationship was not seen for social support. Therefore, rather than all psychosocial factors as hypothesised, it is positive psychological traits alone that may be more important in preventing transition to higher frailty states

Those with a greater PIL and grittier personality traits may be more psychologically robust to withstand age- and health-related stressors that occur in the development and progression of frailty, adapting better to any transitions in health-status. These psychological buffers may be particularly important in how one responds to early frailty changes and hence the distinction between lower and higher risk frailty scores, as frailty represents a gradual process allowing adaptation over time, rather than might be seen for other single diseases states such as cancer. Additionally, their role in early frailty is supported by the finding that psychological factors do not appear to protect against adverse events once one is frail, which may be seen as an end-stage state [480].

The relationship with HRQoL

Frailty has been associated with HRQoL in UK older adults [519]. We have demonstrated that scores for the individual SF-12 HRQoL domains were broadly positive, apart from neutral response for energy/vitality, which was expected given the earlier reported high prevalence of individuals meeting the low energy criterion of the FP within this cohort. Scores on all domains were significantly lower in frail individuals, who reported more positively on components of mental health (mental health, emotional role limitation and the composite MCS). The PCS (48.2) and MCS (48.5) values for the whole cohort are in line with two large HIV trials that had values for PCS and MCS respectively of 48.4 and 44.5 in SMART and 53.6 and 48.1 for START. Though both demonstrated higher scores in physical domains of HRQoL, whereas mental domains were higher in our cohort, particularly among frail individuals [218,219]. These study populations differ however, with high cART use in our cohort and the other two examining treatment interruption and initiation, where people may have had HIV for a shorter duration, be younger, and have less comorbidity. The pattern of higher MCS and lower PCS was also observed with increasing age and duration of HIV in a study of French HIV cohorts [498].

HRQoL for all domains and the two component scores differed significantly across the four frailty categories with QoL decreasing as frailty increased. Higher QoL in all domains was protective for frailty in univariate analysis but after applying our multivariable model better QoL in physical functioning, pain, energy, physical role limitation and the PCS were associated with reduced odds of frailty, with no association for mental health, social function and emotional role limitation. This may not be surprising as we utilised a predominantly physical phenotype of frailty. We discussed the association between frailty and depression in this cohort previously and this further supports a role for identifying emotional and mood problems and potentially for providing interventions to boost emotional well-being and QoL.

It should be acknowledged that the SF12 captures subjective HRQoL based primarily on how one feels about their health and emotional status over the last four-weeks and is therefore open to influence by several factors, which in

previous work has been related to comorbidities and functional limitations rather than HIV-factors suggesting that the impact of HIV directly on HRQoL may diminish with time [497]. We have not assessed wider factors in relation to QoL in this study but these findings may prompt focus on age-related over HIV-related determinants.

Strengths and limitations

The strengths of these analyses are the completeness of responses for each of the included surveys and the examination using standardised measures for all the psychosocial traits examined. There are some limitations however; we only explored the relationship between two psychological traits and frailty in older PLWH and thus we cannot generalise this to other psychological constructs that may be at play, particularly with respect to the hedonic aspects of well-being, or coping strategies which seem important in frailty. Additionally, to assess the relationship with frailty we applied the same logistic model used earlier for potential biomedical predictors, which may not be the most appropriate approach potentially resulting in residual positive or negative confounding, particularly with respect to socioeconomic markers and the influence of psychosocial traits on each other.

Once again the cross-sectional nature restricts our commentary to the current state with regard to grit, PIL and social networks and we cannot say how they have evolved alongside the individual ageing trajectories and at key periods such as around HIV diagnosis, during any AIDS events or at the time individuals became frail; however this latter period is most likely to have been lengthy rather than an acute change that could be attributable to a marked alteration in psychological state, excluding major depressive disorder. Additionally, we cannot comment on causality but it is likely that psychosocial factors are reciprocal in their relationship with frailty.

6.1.5 Conclusion

Clearly psychosocial factors are related to frailty status in this cohort of PLWH and are likely to be of wider importance regarding issues of ageing in the context of HIV outside off frailty. Longitudinal work would allow one to better understand which psychosocial factors have the biggest influence on frailty in PLWH with

focus placed on traits that protect against the development and/or progression of frailty or indeed other age-related problems. This could open the possibility of psychosocial interventions. It would be of interest to know how premorbid psychological traits affect response to receiving an HIV diagnosis and whether robust traits such as grit and PIL influence post-diagnosis behaviours and indeed chance of successful ageing in the presence of chronic HIV infection. Any longitudinal evaluation of the psychosocial influences of ageing within HIV should encompass a generational approach as psychological adaptation, whether successful or not, may vary across those diagnosed in a time of no treatment, high AIDS diagnoses and poor prognosis to current generations with access to speedy diagnostics, early initiation or less toxic ART; accompanied by a change in societal outlook towards HIV and an atmosphere of optimism, where earlier eras of HIV may be seen as more psychologically ‘hostile’.

6.2 Cognitive correlates of frailty in older adults with HIV

6.2.1 Introduction

Healthcare systems and health promotion place emphasis on reducing risk factors and encourage behavioural change to positively influence health status. This has largely focused on physical aspects of health, which may be at the disadvantage of promoting or protecting cognition. Successful cognitive ageing describes ageing in the absence of pathological cognitive impairment and achieving this will become increasingly important due to the predicted rapid expansion of the older population [22,61]. Those with HIV appear particularly vulnerable to abnormal cognitive decline due to the effects of HIV, its treatments and the additive influences of normal ageing.

Cognitive frailty

The relationship between cognition and physical frailty has been gaining increasing attention as researchers try to investigate the complex interacting process occurring during ageing and what differentiates those on more positive and negative ageing trajectories.

Using data from the Canadian Study of Health and Aging of community-dwelling older adults aged over 70, Mitnitski et al. demonstrated that increasing frailty was associated with increased cognitive impairment irrespective of the frailty measure used (FP, FI and the Clinical Frailty Scale). Here, the frailest showed low rates of cognitive improvement or stabilisation at 1.5% in five years compared 27.8% in non-frail individuals suggesting a steeper cognitive decline in the most frail [454].

In a 12-year longitudinal study of cognitively intact community-dwelling older adults drawn from residential settings in Chicago, Boyle et al. showed that 40% developed mild cognitive impairment (MCI) over that period. Baseline frailty increased the likelihood of first expression of MCI by 63% (HR 1.63 95% CI 1.27-2.08) with association persisting after controlling for depression, disability and vascular disease [505]. In this same cohort, baseline frailty predicted incident Alzheimer's disease at 3 years with rate of change of FP score associated with change in cognition, suggesting that frailty is associated with rate of cognitive decline and precedes dementia [520]. This prompted the authors to suggest that Alzheimer's neuropathology may potentially have an effect on gait and muscle

before reaching a threshold for cognitive impairment [520]. Baseline frailty has also been shown to predict incident cognitive impairment in further longitudinal studies [451,521,522], and the inclusion of cognitive impairment to physical frailty is shown to improve the predictive ability for adverse outcomes [112,451].

These associations between frailty and cognitive impairment plus the finding that premorbid cognition predicted incident frailty at 10 years follow-up in a cohort of older Mexican Americans [523] and at 5 years in the English Longitudinal Study of Ageing [524] demonstrates the inter-relatedness of cognitive impairment and physical frailty. Frailty increases the risk of cognitive decline and cognitive impairment increases the likelihood of physical frailty [525]. This suggests there may be some shared aetiology or pathways between the two. However, it is unknown whether the trajectory of frailty that begins with cognitive impairment is the same as the trajectory for frailty that begins with physical deficits [452].

To try and formalise this relationship a consensus definition of cognitive frailty was proposed in 2013 by the International Academy on Nutrition and Aging and the International Association of Gerontology and Geriatrics. They describe it as heterogeneous state distinguished by the simultaneous occurrence of both physical frailty and cognitive impairment which does not meet the criteria of Alzheimer's or any other dementia subtype [526]. The degree of cognitive impairment should equal 0.5 on the Clinical Dementia Rating Score, corresponding to 'very mild' symptoms. A psychological component that reduces one's resilience to stressors may contribute [526]. Cognitive frailty may represent pathological brain ageing and an antecedent to neurodegenerative processes though the causal pathways connecting cognitive and physical frailty are unknown.

Cognitive reserve

Both successful cognitive ageing (SCA) and cognitive frailty may depend upon the degree of both brain and cognitive reserve, for which authors have taken the analogy of computer hardware and software [527]. Brain reserve is akin to computer hardware concerning gene influence on innate brain structure and capacity, and subsequent structural and functional changes such as volume loss, disorganisation of white matter tracts and overt brain pathology (e.g. strokes) may

impact cognition when a critical threshold of (irreversible) damage is reached. Cognitive reserve represents the software, where there is an acquired level of resilience for and active compensation to age-related and pathological brain changes. This mediated through better use of resources such as recruiting alternate neural pathways and shifting functions away from specific hemispheres as well as using external cognitive mechanisms [527]. Cognitive reserve reflects the ability of an individual to minimise or avoid cognitive impairment and may explain why two individuals of differing cognitive reserve may have divergent outcomes in terms of NCI from the same brain insult, such as a stroke. These two reserve mechanisms probably act in parallel to maintain cognitive function into later life [527]

Cognitive reserve may be fixed once you reach later life with a large component established through early life experiences, particularly greater education, occupational attainment and active leisure time-activities [528]. However, it is theorised that engaging in intellectually stimulating activities can protect against cognitive decline in a “use it or lose it” fashion [529].

Factors that promote cognitive reserve, which represents the potentially modifiable component of cerebral reserve, may in turn help to promote SCA and prevent cognitive frailty. The factors associated with these concepts appear to overlap and include higher socioeconomic status; positive psychosocial factors; resilience; positive physical and mental health behaviours including physical activity and avoidance of smoking and drug and alcohol misuse; and the absence of negative biological predictors such as APOE-ε4 genotype and psychiatric diagnoses, particularly depression [528,530,531]

Cognitive impairment in HIV

HIV is a neuroinvasive virus, which enters the central nervous system (CNS) via infected mononuclear cells and then replicates within macrophages, microglial cells and to a lesser extent astrocytes. Replication promotes immune activation, viral protein production and inflammation which all have neurotoxic effects, as well as increasing blood-brain barrier permeability and amyloid deposition in a pattern atypical for Alzheimer’s disease thus differentiating their neuropathologies [532].

Neurocognitive impairment (NCI) has been a significant issue throughout the HIV epidemic, which though reduced with the advent of effective cART persists in current HIV cohorts. In 2007 to better reflect the spectrum of NCI seen clinically and on neuropsychological (NP) testing the HIV Neurobehavioral Research Centre proposed new diagnostic criteria. Often referred to as the Frascati criteria they describe three stages of HIV-associated neurocognitive disorders (HAND) [533]:

1. Asymptomatic neurocognitive impairment (ANI), if demonstrable (mild) cognitive impairment on neuropsychological testing (>1sd below population norm in at least two cognitive domains) which does not impact on everyday functioning
2. HIV-associated mild neurocognitive disease (MND), where cognition is impaired as in ANI with at least mild impact of everyday functioning.
3. HIV-1-associated dementia (HAD), in those with marked acquired cognitive impairment usually across multiple domains (>2sd below population norm in at least two cognitive domains) with significant impact on day-to-day functioning (work, home life, social activities).

The above all rely on the absence of delirium; dementia in ANI or MND or an alternative dementia subtype for those with HAD; or any other pre-existing cause for the cognitive impairment. Pre-existing or alternative causes for cognitive impairment may include opportunistic infections or conditions unrelated to HIV affecting the CNS such as stroke or traumatic brain injury; co-infections particularly hepatitis C; and drugs with CNS side effects [533]. These criteria were compared to post-mortem examination for HIV encephalitis demonstrating a positive predictive value of 95%, sensitivity of 67% and specificity of 92%, which were all higher than those achieved using the previous 1991 American Academy of Neurology criteria [534].

Epidemiology of NCI in the cART era

Widespread use of cART has certainly influenced HIV-related NCI. The distribution of HAND has shifted with reductions in the prevalence of HAD, which has reduced from 10-15% pre-ART to <5% post cART introduction [535,536].

However, the incidence and prevalence of lesser degrees of HAND have remained static or even increased [532,537,538]. Prevalence of NCI based on the Frascati criteria is highly variable ranging from 18-74% [537,539–544], with Simoni et al. using their data to suggest that the general HIV-population prevalence for those on suppressive cART may be as high as 69% [537]. This variation probably represents the heterogeneous populations studied, particularly with respect to degree or cART usage and viral suppression achieved.

The UK POPPY study provides the closest population to that seen in our cohort. They examined cognition using three methods in 290 HIV-positive adults over 50 with a demographically comparable HIV-negative control group (n=97). Depending on the cognitive screening tool used the prevalence of NCI was significantly higher in those with HIV ranging from 22.1-34.5% and 7.2-16.5% if HIV-negative. In HIV-positives the prevalence based on HAND criteria was 30% [539]. In POPPY 90.7% of those on cART were virally suppressed compared to 44% in the CNS HIV Antiretroviral Effects Research (CHARTER) study of 1555 PLWH recruited from six US university clinics in whom 52% exhibited NCI. This prompted the authors to suggest that active viral replication may promote ongoing CNS inflammation and in turn HAND [544].

However, HIV is not always a significant predictor, as in a cohort followed longitudinally over 18 months those with HIV demonstrated a greater but not statistically significant decline in cognition compared to HIV-negative controls (14 versus 5%, p=0.11) [541]. Additionally, other virally suppressed populations with closely matched HIV-negative subjects have not shown any difference in NCI [542,543,545].

The presence of NCI in PLWH and an increasing severity of HAND have been associated with worsening HRQoL [546,547] and performance on both subjective and objective tasks of physical functioning, including higher levels of unemployment, reduced financial capabilities [546,548]. As well as risk of medication mistakes including significantly poorer adherence to cART regimes, especially in older adults [546,549].

Despite the high prevalence of HAND, of which the majority is ANI [538,541,544,550], there is criticism of the classification [537,551]. The recorded high prevalence may be an overestimation, secondary to a failure to utilise appropriate demographic normative data, especially with respect to ethnicity [543,552]; or misclassification of those who naturally exist on the low end of cognitive functioning to have HIV-related NCI [551]. Though ANI is associated with higher likelihood of progression to symptomatic HAND and poorer outcomes [550,553] a robust screening tool for ANI in the clinical setting is lacking. Therefore, without a consensus monitoring or treatment strategy over and above universal cART initiation, achieving a diagnosis may be invasive and costly with potential for psychological harm [551,552]. It should be noted however that there has been increasing attention in classifying Alzheimer's dementia as a spectrum encompassing an asymptomatic stage in an effort to identify potential targets for intervention, given the poor therapeutic outcomes achieved at symptomatic stages in halting cognitive decline [554]. Lastly though significant differences have been demonstrated in cognitive scores between positive and negative controls or between different treatment groups one must be mindful that these may fail to reach a clinically relevant difference [539].

The role of HIV and cART on NCI

As illustrated, cART is ameliorating the burden of NCI in HIV. However, in groups with mixed exposure to cART HIV factors have been associated with poorer performance on NP tests, particularly low current CD4, prior AIDS diagnosis, detectable VL and longer duration of HIV [536,555]. More severe immunosuppression is associated with increased risk of HAND, with low nadir CD4 (<200) the most consistently reported predictor of NCI [532,537,538,544]. The authors of the CHARTER study introduce the idea that a low nadir CD4 may be a "legacy event" in that any consequences of advanced immunosuppression may be irreversible, persisting long-term, particularly with respect to cognition [544]. This hangover from previous immune damage, as well as failure of viral suppression within the CNS due to issues of drug penetration, presence of resistant viral subtypes in the CNS, or neurotoxicity of ART, may partly explain the persisting prevalence and ongoing incidence of HAND even in the presence of cART [538]. Alternatively, cART may

suppress viral replication but not dampen immune activation or inflammation as was seen in a group of HIV-positive individuals with NCI on suppressive cART [545].

In well treated cohorts HIV and HIV factors have been shown to have little [540,542] or no impact on cognitive decline [537,541,546,556]. In those on cART achieving viral suppression and in the absence of viral escape denoted by detectable viral RNA within the CSF, viral replication is unlikely the major driving force for HIV-related NCI. Additionally, it is debated whether cART contributes to NCI by causing neurotoxicity either directly or more likely indirectly through metabolic adverse effects [537,551].

It is important to consider non-HIV aetiologies including an increasing burden of comorbidities, particularly vascular disease; as well as drug or alcohol misuse, hepatitis C co-infection and other age-related neurodegenerative diseases, which may contribute to HIV-related NCI [544,552,553]. Concurrent depression may particularly confound the relationship between HIV and NCI. Diagnosed major depressive disorder was shown to be associated with poorer performance on a range of cognitive domains on NP testing and higher levels of self-reported cognitive symptoms in PLWH [557]. Additionally, there may be differences in the aetiology between younger and older PLWH as demonstrated by Fogel et al. who showed that recreational drug misuse predicted HAND and global cognitive scores in younger individuals and dyslipidaemia in the older group, supporting the role of cerebrovascular disease [558]. Age has not been seen as a major predictor of NCI in HIV [533,538,544,559]; however, age remains the biggest risk factor for non-HIV-associated neurodegenerative diseases and as one ages there is increasing overlap between risk factors for cognitive impairment, provoking the need to consider more ‘traditional’ causes of cognitive decline, particularly as the cohort entering later old age grows [560]

Neuropsychological deficits in HIV

NCI may be subtle in HIV with changes in concentration, attention, comprehension, working memory or mental slowing [532,561,562]. NCI, particularly ANI may be difficult to detect clinically as cognitive change may be slow, allowing for unconscious compensation, or it may be unperceived, especially in retirees or

those out of work in whom cognitive demands may be lower. Additionally, transition to higher degrees of HAND may not be easily detected due to failure to recognise functional difficulties, which are often subjectively self-reported [561]

On NP testing, HIV appears to affect several cognitive domains as a result of more diffuse CNS injury compared to other causes of NCI [541,553]. However, a meta-analysis showed that the pattern of NCI in those with HIV is primarily subcortical with greatest changes seen in psychomotor speed and executive skills with memory and visual perception less affected [562]. This has been supported by other work, particularly confirming reduced psychomotor speed as a core deficit [539,541,542,553]; as well as showing poorer performance in episodic memory (particularly prospective memory), attention, verbal learning and executive function [539,541,553], with mixed effects for motor control [541,542]. Older age has been associated with poorer performance on NP testing than younger PLWH irrespective of cognitive status, especially scoring lower in tests of verbal memory, visual memory, verbal fluency and psychomotor speed [563,564], though others have seen no clinically relevant additive or interacting effects of age in PLWH aged under 60 with a paucity of data in older groups [565].

This pattern of cognitive impairment is said to be subcortical in nature corresponding to neuropathological damage in subcortical structures such as the white matter of the frontal lobe, the fronto-striatal and parieto-striatal pathways and basal ganglia [541,553,562], with other demonstrating reduced total brain and thalamic volumes [542]. Additionally, compared to HIV-negative subjects PLWH demonstrated MRI evidence of faster ageing trajectories shown by volumetric loss in a number of brain regions, which were slowed by the initiation of cART [566]. However, changing cognitive patterns observed in investigation of NCI in the cART era have shown poorer performance in memory and executive function prompting some to suggest a shift towards a more cortical type dementia as typified by Alzheimer's [537,538]. Though this cortical shift was not demonstrated in a study examining the interacting effects of age and HIV on NP profile of NCI [564].

Cognitive reserve and successful cognitive ageing in the context of HIV

HIV appears to affect cognitive functioning, which remains prevalent despite cART. There is an anticipation that the situation will both increase in size and

complexity as the effects of HIV and usual age-related challenges to cognition combine.

Cognitive reserve has been examined in the context of HIV, with higher reserve appearing to protect against the neuropathological effects of HIV as demonstrated by higher scores on NP testing compared to those with low reserve [567–570]. Foley et al. hypothesised that those at highest risk of NCI were older adults with HIV as they faced the combined effects of age and chronic HIV. In older PLWH without NCI, cognitive reserve measured using a composite score of education and word-reading ability, was significantly higher than younger HIV-positives and older HIV-negatives [569]. Younger age and higher cognitive reserve combined to provide a neuroprotective effect that was independent of measured HIV, mood and psychosocial factors. This suggests that higher cognitive reserve is protective against NCI in HIV, especially at older ages [569].

Fazeli et al. examined the relationship between active lifestyle factors (ALF) of physical exercise, social activity and current employment as a proxy for cognitive reserve, and NCI in 139 American PLWH (mean age 48.7). They demonstrated that a higher number of ALF was associated with higher global NP performance and lower prevalence of HAND. This decreased in stepwise fashion from 63% in those with no ALFs to 20% in those with all three, suggesting that partaking in a range of lifestyle activities may offer the most protection against NCI in PLWH [571]. However, the authors acknowledge the cross-sectional methodology and the inverse possibility that higher NCI may allow one to engage in such activities [571]. Further studies have supported the protective role of physical exercise against NCI in PLWH [397,572]

SCA has also been examined in the context of HIV and frailty. When operationalised as ageing in the absence of NCI it was achieved in 39% of 102 HIV-positive participants on virally suppressive cART regimens in Italy. Age and CD4 (nadir and current) were not associated with SCA but frailty was, with each additional deficit on their frailty index associated with a 12% reduction in the odds of achieving SCA (OR 0.88, p=0.04) [556]. Additionally, in a group of 302 individuals with and without HIV recruited to the HIV Neurobehavioural Research Program in San Diego, SCA defined as normal scores on both NP testing and self-reported

cognitive functioning was lower in those with HIV (24.9% vs 40.0%), and lowest in older adults with HIV (>50 years) at 20%. SCA was not associated with HIV factors but was predicted by higher cognitive reserve [531]. Lastly, 32% of 74 middle-aged PLWH (mean age 51) were deemed to have SCA, which was associated with lower major depressive disorder, and significantly greater ability to manage medicines and interact with health services, adherence and everyday ADL functioning compared to those without SCA. Importantly HIV factors were not associated with SCA [573].

These data suggest that cognitive reserve, which has been linked to cognitive frailty and SCA may be important in the development of NCI in PLWH and as such warrants further investigation.

Aims and Hypotheses:

There has been very little examination of the role of cognition in the context of frailty in PLWH. Therefore, the aim of this second section is to describe both subjective and objective markers cognitive function in relation to frailty status. The prospective and retrospective memory questionnaire (PRMQ) allows participants to self-rate their memory in terms of everyday memory usage and mistakes. Formal objective testing of a global cognitive screen utilised the Montreal Cognitive Assessment (MoCA) alongside tests of specific cognitive domains.

In line with the aims of this chapter we set the following hypotheses.

Hypothesis 1: Cognitive performance both self-rated and objectively measured will be lower in those with frailty compared to non-frail individuals, with cognitive function worsening as frailty increases.

Hypothesis 2: In line with findings regarding psychosocial traits, cognitive dysfunction will increase as level of frailty increases with prefrail individuals representing an intermediate group, who based on their FP score can be identified as being closer to robust or frail states in terms of their cognitive abilities.

6.2.2 Methods

All 253 participants were asked to engage with the cognitive or 'memory' based aspects of the study. The PRMQ was embedded within the study questionnaire and completed with the other battery of questionnaires.

The additional neurocognitive battery was contained within a separate template booklet, which aimed to standardise order of testing. Following questionnaire completion participants were asked to complete the computer-based simple reaction time test and then the other cognitive tasks completed in the order of the National Adult Reading test, the Montreal Cognitive Assessment (MoCA), the controlled oral word association test, in the form of the F-A-S test, finishing with the Trails Making Test (TMT). Ordering was introduced to maintain consistency between participants with testing biases reduced by all tests being administered by the same examiner. Full details of the individual tests are provided in chapter three, with summary details and rationales outlined below.

Prospective and retrospective memory questionnaire (PRMQ) [208]

Prospective memory relates to the timing of when things are remembered and retrospective memory on what should be remembered. The PRMQ is a 16-item self-report tool measuring failures in pro- and retrospective memory in everyday life. Prospective and retrospective memory are represented by eight statements each, with each memory mistake rated on a five-point scale corresponding to numerical scores ranging from occurs very often (scores 5) to never occurs (scores 1). Scores are summed to provide a total score, with minimum and maximum possible total scores of 16 and 80, respectively. The PRMQ provides total, prospective and retrospective memory scores with higher scores representing a worse assessment of memory.

Neuropsychological battery

National Adult Reading Test (NART) [211]

The NART estimates premorbid intelligence. The test comprises 50 words with irregular pronunciation printed in order of increasing difficulty and read aloud with the number of pronunciation errors recorded. Scores are then used to predict

intelligence quotient (IQ) using the formula: IQ= 127.7 – (0.826 x Number of errors) [211].

Trail making test (TMT) [212]

The TMT can be used to measure several cognitive domains including processing speed, sequencing, mental flexibility and visual–motor skills. It is a timed paper and pencil task comprising two parts: In part A (Trails A) the participant was instructed to connect a sequence of 25 randomly distributed encircled numbers in ascending order (e.g. 1-2-3-4 and so on). In part B (Trails B) encircled letters were introduced randomly amongst the numbers with participants instructed join the numbers and letters in sequential fashion (e.g. 1-A-2-B-3-C and so on). Both parts were timed, with error correction incorporated within the task time. A recognised upper cut-off time of 300 seconds was applied as the maximal time for completion. Psychomotor speed differences were indicated by performance on TMT A, therefore to minimise the influence of processing and psychomotor speed on executive function as assessed by TMT B, a ratio of B/A (TMT ratio) was calculated [236].

Controlled Oral Word Association Task (COWAT) [213,237]**.**

The controlled oral word association task (COWAT) assesses verbal fluency. The F-A-S form of the test was utilised with participants given one minute to verbalise as many words as possible beginning with each of these three letters of the alphabet. Participants were instructed to avoid proper nouns (e.g. France, Frederick), numbers or saying the same word with a different ending (e.g. fight, fights, fighting). The number of valid words for each of the three letters was summed to give the total score for analysis.

Simple reaction time (SRT):

The SRT is a classic test of psychomotor speed measuring reaction time through use of a computer based test. Participants were asked to detect the stimulus, the appearance of an ‘X’ in place of a plus sign in the centre of the screen, and respond by pressing the ‘space bar’ on the keyboard as quickly and accurately as possible. The stimulus occurred at varying time intervals, unpredictable to the participant; in this case the task consisted of a total of 48 trials, with a mask of varying length (300ms-1000ms) present between each target stimulus. All

participants completed a practice task before moving on to the main scored task. RTs greater or less than 3 standard deviation (SD) from a participant's mean RT were removed prior to analysis.

Montreal Cognitive Assessment (MoCA) [210]

The Montreal Cognitive Assessment is an open-access, one-page 30-point test of multiple cognitive domains: short-term memory, visuospatial ability, executive function, attention, concentration, and working memory, language and orientation. The score was adjusted for education of 12 years or less by addition of one point to the total, up to the maximum score of 30. A test score of 26 and above is normal, with scores <26 used to define cognitive impairment in this cohort.

Neurocognitive battery rationale

HAND can present with a diverse range of impairments across many cognitive domains though the pattern of NCI is predominantly subcortical in nature. Therefore, tasks were included to examine core areas of cognition that are particularly vulnerable to dysfunction in PLWH to assess their relationship with frailty. Cognitive domains tested include speed of information processing (SRT and TMT part A); executive functioning deficits in planning, handling complex problems and task switching (TMT part B); verbal fluency, a commonly used measure of executive function, and the most common language deficit seen in HAND (COWAT); memory, which in HAND especially affects prospective memory and learning of new information (PRMQ and MoCA). The MoCA allows for testing of individual domains including attention and working memory as well as global memory. These cognitive functions do not exist in isolation and will clearly impact on each other if impaired, particularly with respect to mental slowing and executive dysfunction.

It is recommended that five cognitive domains are examined to make formal diagnoses of the HAND conditions, however this was not the intention here, where our primary motive was to provide an initial exploration of potential NCI differences between frailty subgroups. As such we did not include a larger number of cognitive function tests and will not be classifying individuals by HAND status.

Statistics

All analyses were performed utilising the statistical methods outlined at the beginning of this chapter for psychosocial data.

6.2.3 Results

Full data on all 253 participants was available for the PRMQ, MoCA, and COWAT. Two participants failed to complete the NART and TMT, both of whom were frail, giving a denominator of 251 (99.2%) for analyses of these variables. There was greatest missing data for the SRT, which was completed by 236 participants (93.3%) representing 191/205 (93.2%) non-frail individuals and 45/48 (93.8%) for frail. Failure to complete the SRT reflected technical issues rather than participant inability. Once again, core analyses used the predefined frail versus non-frail groups, with hypotheses regarding trends across frailty using the four frailty groups previously defined (robust, prefrail A, prefrail B and frail).

Neurocognitive factors: frail versus non-frail

Table 6.7 shows the scores of all neurocognitive factors for the full cohort and divided by frail and non-frail groups. There was no statistical difference in premorbid intelligence as assessed by number of errors on the NART and corresponding calculated IQ. This allows assessment of NCI to be completed with greater confidence that premorbid differences are not confounding relationships between frailty groups. Those with frailty had lower subjective memory ability with significantly lower mean scores on the overall PRMQ ($t(251)=-5.68$, $p<0.001$) and both the prospective ($t(251)=-5.52$, $p<0.001$) and retrospective components ($t(251)=-5.18$, $p<0.001$) when compared to non-frail individuals. Frail individuals also had significantly lower objective cognitive functioning based on the MoCA, $z=2.41$, $p=0.016$, with a higher proportion meeting the criteria (MoCA<26) for cognitive impairment at 35% versus 19%, $X^2=(252,N=253)=6.51$ $p=0.011$.

Median reaction time was significantly slower in those with frailty, $z=-4.28$, $p<0.001$, who also had poorer performance on both the TMT-part A, $z=-2.35$, $P=0.019$ and part B, $z=-2.89$, $p=0.004$. No difference was seen in the TMT-ratio of B/A, $z=-1.535$, $p=0.125$, suggesting that the source of the TMT differences was processing speed rather than differences in executive skills. Frail individuals demonstrated significantly lower verbal fluency on the COWAT, ($t(251)=2.12$,

p=0.035). As predicted in our first hypothesis, frail individuals performed worse on all the included cognitive markers, when matched on baseline intelligence.

Table 6.7: Neurocognitive scores across the full cohort and by non-frail and frail groups

Variable	Full cohort N=253 (%)	Non-Frail N=205 (%)	Frail N=48 (%)	Test Statistic	*p* [a]
IQ [b] (n=251)	117.0 (111.2-120.3)	117 (112.0-120.3)	117 (111.2-118.6)	0.967	0.333
NART errors [b]	13 (9-20)	13 (9-19)	13 (11-20)	-0.967	0.333
PRMQ [c]	38.6 (12.2)	36.6 (11.2)	47.1 (12.7)	-5.680	**<0.001**
Pro PRMQ [c]	20.5 (6.7)	19.4 (6.1)	25 (7.1)	-5.523	**<0.001**
Retro PRMQ [c]	18.1 (6.2)	17.2 (5.8)	22.1 (6.4)	-5.181	**<0.001**
MoCA [b]	27 (26-29)	27 (26-29)	26.5 (24-28)	2.414	**0.016**
Cognitive impairment	55 (21.7)	38 (18.5)	17 (35.4)	6.514	**0.011**
Reaction time (msecs) [b]	334 (287-418)	325 (285-392)	400 (318-561)	-4.280	**<0.001**
TMT-A (secs) [b]	34.3 (28.1-43.7)	33.7 (27.8-42.5)	38.4 (30.4-52.5)	-2.346	**0.019**
TMT-B (secs) [b]	80.2 (62.4-111.6)	78.5 (60.8-105.5)	93.4 (71.6-130.9)	-2.893	**0.004**
TMT-ratio (B/A) [b]	2.31 (1.84-2.86)	2.28 (1.83-2.85)	2.47 (2.10-2.87)	-1.535	0.125
COWAT [c]	39.4 (12.9)	40.2 (13.0)	35.9 (11.8)	2.118	**0.035**

[a] p-value based on X^2 test unless stated.
[b] median (IQR); p-value based on MWU test providing z-statistic.
[c] mean (sd); p-value based on two-way t-test providing a t-statistic

Subjective and objective global memory (four frailty groups):

The results of one-way ANOVA analyses of PRMQ across the four frailty groups are shown in Table 6.8. Violation of assumptions called for log (natural) transformation of retrospective PRMQ scores prior to ANOVA. The mean PRMQ score increased with higher frailty state which was statistically significant using one-way ANOVA ($F(3,249)=20.49$, $p<0.001$), meaning that frailer individuals reported more memory mistakes. We applied a post-hoc Tukey HSD test, which showed no statistical difference between those individuals classed as prefrail A compared to robust (2.77, p=0.434) or in those with frailty compared to prefrail B

(4.14, p=0.236). After Bonferroni adjustment, all other pairings were significant, prefrail B compared to robust (9.63, p<0.001), frail compared to robust (13.77, p<0.001), frail compared to prefrail A (11.0, p<0.001); as well as between the two prefrailty groups (6.86, p=0.007). Therefore, those in the robust and prefrail A groups were more similar, and significantly different to the prefrail B and frail groups that were more similar to one another.

The mean scores for both prospective and retrospective memory tasks worsened significantly with higher frailty states as demonstrated by use of one-way ANOVA with respective values for prospective (F(3,249)=18.48, p<0.001) and retrospective components (F(3,249)=15.44, p<0.001). Post-hoc Tukey tests showed the same pattern for the overall PRMQ, with no significant differences between prefrail A and robust, and frail and prefrail B pairings. There was no significant difference between prefrail A and B groups for either prospective or retrospective scores but all other pairings were statistically different with all p-values <0.001.

Table 6.8: The distribution of PRMQ scores across the four predefined frailty groups

Variable Mean (sd)	Robust N=94	Pre-frail A N=58	Pre-Frail B N=53	Frail N=48	F (3,249)	*p* [a]
PRMQ	33.33 (9.51)	36.10 (9.70)	42.96 (13.02)	47.10 (12.72)	20.49	**<0.001**
Pro PRMQ	17.76 (5.59)	19.05 (5.16)	22.68 (6.88)	25.00 (7.05)	18.48	**<0.001**
Retro PRMQ [b]	14.92	16.30	19.05	21.14	15.44	**<0.001**

[a] p-value based on one-way ANOVA
[b] ANOVA following log transformation secondary to violation of assumptions

Table 6.9 describes the global objective assessment of cognition across the four frailty groups. MoCA scores were skewed with transformation failing to correct variances to allow for one-way ANOVA therefore a Kruskal-Wallis test was performed demonstrating a statistically significant difference across the groups with median MoCA scores decreasing as frailty increased (X^2(3, n=253)=13.75, p=0.003). Post-hoc pairwise ranks-based comparisons only demonstrated a

significant difference between frail and robust groups (p<0.001), suggesting no obvious groupings regarding the four frailty categories. The proportion of those with cognitive impairment increased as frailty increased with significant difference across the groups by chi-squared test (X^2(3, n=253)=12.22, p=0.007).

Table 6.9: The distribution of MoCA scores and degree of cognitive impairment across the four frailty groups.

Variable Mean (sd)	Robust N=94	Pre-frail A N=58	Pre-Frail B N=53	Frail N=48	X^2 (3,249)	*p*
MoCA	28 (26-29)	27 (26-28)	27 (25-29)	26.5 (24-28)	13.75	0.003 [a]
Cognitive impairment	11 (11.7)	12 (20.7)	15 (28.3)	17 (35.4)	12.22	0.007 [b]

[a] p-value based on Kruskal-Wallis test
[b] p-value based on chi-squared test

Additional tests of neurocognitive functioning (four frailty groups):

Median reaction time increased across the frailty groups, though the reaction time was slightly slower in the prefrail A than prefrail B group as shown in Table 6.10. There was a significant difference in psychomotor speed demonstrated across the four groups using the Kruskal-Wallis test (X^2(3, n=236)=28.16, p<0.001). In post-hoc pairwise analyses frail individuals had significantly slower reaction times than robust (p<0.001) and prefrail-B (p=0.005) but not prefrail-A (p=0.009). The prefrail-A group was significantly slower than robust (p=0.003). All other pairings failed to reach statistical significance. Again, there is no clear evidence of grouping of lesser and higher frailty states.

Table 6.10: Differences in median reaction time across the four frailty groups (n=236)

Variable Median (IQR)	Robust N=87	Pre-frail A N=55	Pre-Frail B N=49	Frail N=45	X^2 (3,233)	*p* [a]
SRT (msecs)	304 (268-348)	349 (288-467)	342 (292-398)	400 (318-561)	28.16	**<0.001**

[a] p-value based on Kruskal-Wallis test

Table 6.11 shows the results of the COWAT and TMT across the four frailty categories. Mean number of words generated in the COWAT decreased as level of frailty increased. The group difference was statistically significant using one-way ANOVA ($F(3,249)=2.75$, $p=0.043$). Post-hoc pairwise analysis (Tukey) showed no statistically significant difference between any pairing regarding the total COWAT score: frail-robust (-6.21, $p=0.033$); frail-prefrail A (-3.10, $p=0.559$); frail-prefrail B (-2.42, $p=0.776$); prefrail B-prefrail A (-0.68, $p=0.992$); prefrail B-robust (-3.79, $p=0.313$) or between prefrail A-robust (-3.11, $p=0.466$) after Bonferroni adjustment.

Time to complete the TMT-part A task increased as frailty increased, with difference across the group being statistically significant using one-way ANOVA following log (ln) transformation ($F(3,247)=4.67$, $p=0.003$). The only difference seen on post-hoc Tukey analysis was between frail and robust groups ($p=0.007$). There was no significant difference seen across the groups for the relationship between TMT-ratio and frailty group on one-way ANOVA ($F(3,247)=0.25$, $p=0.859$).

The distributions of the differences in the neurocognitive parameters by the four frailty groups is summarised in Figure 6.3.

Table 6.11: Distribution of COWAT and TMT scores across four frailty group.

Variable Mean (sd)	Robust N=94	Pre-frail A N=58	Pre-Frail B N=53	Frail N=48	F	*p*
COWAT	42.11 (13.17)	39.0 (14.14)	38.32 (11.22)	35.90 (11.83)	2.75	**0.043** [a]
TMT-A (secs) [b]	32.21	36.38	38.07	39.51	4.67	**0.003**[c]
TMT-ratio	2.46 (1.02)	2.47 (0.94)	2.43 (0.77)	2.58 (0.77)	0.25	0.859 [c]

[a] p-value based on one-way ANOVA N=253 (F 3,249)
[b] log transformed (natural log)
[c] p-value based on one-way ANOVA N=251, Frail N=46 (F 3,247)

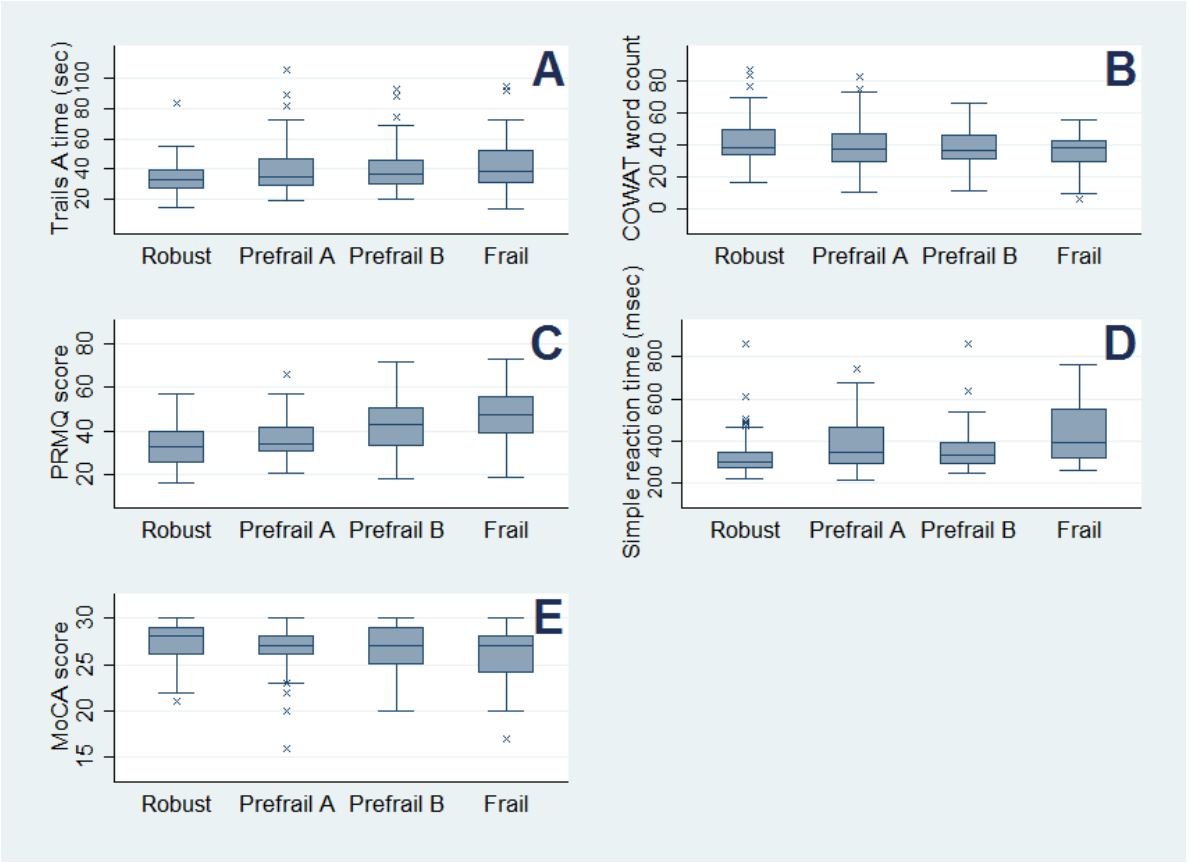


Figure 6.3: Distribution of median scores for neurocognitive tests across four frailty groups. Depicting change by frailty status for A) TMT-part A B) Total COWAT score C) Total PRMQ score D) Simple reaction time and E) MoCA score

Associations between neurocognitive factors and frailty

We applied logistic regression to investigate the association between neurocognitive factors and frailty as shown in Table 6.12. All examined neurocognitive factors were significantly associated with the odds of frailty in univariate analysis, with higher MoCA and COWAT scores protective for frailty. Longer time to complete the TMT, slower reaction time, higher PRMQ score and MoCA defined cognitive impairment were associated with increased odds of frailty.

A higher subjective report of memory impairment for future tasks as assessed by a one-point increase in the prospective PRMQ was associated with a 7% increase in the odds of frailty (aOR 1.07; 95%CI 1.00-1.14, p=0.038). The only other factor associated with frailty was psychomotor speed, where the odds of frailty increased by 49% for every 50msecs increase in reaction time (aOR 1.49; 95%CI 1.05-2.14, p=0.026). It should be noted that the relationship between reaction time and frailty strengthened after controlling for confounding variables suggesting it may have an important independent predictive role in frailty. However, in multivariable analysis controlling for age, sex, HADS score and number of comorbidities, TMT-parameters, cognitive impairment, and higher scores on the MoCA, COWAT and total and retrospective PRMQ were no longer associated with frailty. To ensure that one point changes were not too small a measure of effect we also assessed these variables by quartile change, again showing no significant effect (data not shown further).

Table 6.12: Univariate and multivariable analysis of the role of neurocognitive factors on the likelihood of frailty compared to a non-frail reference group.

		Association with frailty		
Variable	**Crude OR (95% CI)**	**aOR [a]**	**95% CI**	**p-value**
PRMQ	1.07 (1.04-1.10)**	1.03	1.00-1.07	0.062
Pro PRMQ	1.14 (1.08-1.20)**	1.07	1.00-1.14	**0.038**
Retro PRMQ	1.13 (1.07-1.20)**	1.05	0.98-1.12	0.168
MoCA	0.84 (0.75-0.94)*	0.94	0.82-1.08	0.370
Cognitive impairment	2.41 (1.21-4.80)*	1.20	0.50-2.92	0.681
SRT per 50msec	1.24 (1.12-1.38)**	1.49	1.05-2.14	**0.026**
COWAT	0.97 (0.95-1.00)*	0.99	0.95-1.02	0.385
TMT-A (per sec)	1.02 (1.00-1.04)*	1.00	0.98-1.03	0.847
TMT-ratio	1.15 (0.83-1.61)	1.01	0.64-1.60	0.953

[a] Adjusted for age, sex, HADS score and comorbidity count
* p<0.05; ** p<0.001

6.2.4 Discussion

In keeping with our first hypothesis, those with frailty reported greater memory mistakes and performed worse in global and domain-specific cognitive tests despite no difference in baseline intelligence. Significant differences are noted across the frailty groups with cognitive function worsening in all tests. Even after controlling for age, sex, HADS score and number of comorbidities slower reaction time and reporting mistakes in prospective memory tasks predicted frailty.

Self-reported prospective and retrospective memory

We observed that self-reported scores on the PRMQ and both its pro- and retrospective subscales were significantly higher in frail compared to non-frail individuals, and scores worsened, indicating greater memory mistakes as frailty increased. Worse prospective memory was associated with a 7% increased likelihood of frailty after controlling for potential confounders. Reporting of cognitive complaints is not uncommon in PLWH, particularly regarding episodic memory and memory mistakes, as reflected in the self-report PRMQ [574,575]. Episodic memory is made up of retrospective memory (RM) and prospective

memory (PM). RM constitutes the recall of past events and experiences, usually in response to a prompt whereas prospective memory (PM) concerns 'remembering to remember' a future intention in the absence of prompts, such as remembering to attend a hospital appointment at a given time and date. PM plays a crucial role in tasks of everyday functioning, in employment and importantly treatment adherence, as one must remember to take medications at the prescribed time [576].

PM is thought to be a cognitive facet of intact frontal lobe structures and fronto-striatal pathways, which are a target for HIV-associated NCI. Carey et al. showed poorer PM in a group of 42 well-treated PLWH compared to 29 demographically similar seronegative controls, with those with impaired PM demonstrating a higher likelihood for NCI on formal NP testing [574]. Others have shown an increase in both PM and RM complaints in those with HIV compared to HIV-negative controls, with self-reported PM complaints more common and more severe than for RM [577], which is in keeping with our findings in relation to frailty status. PM complaints, including those assessed using the PRMQ have been shown to independently predict poorer medication adherence [578] and difficulties in instrumental ADLs in PLWH [579], which are thought to be more cognitively rather than physically demanding [580]. PM is therefore essential in everyday functioning, avoiding disability and maintaining independence and autonomy. It is possible that this interaction between PM and functional decline could be mediated by frailty, though there is no published literature that directly addresses PM in terms of physical or cognitive frailty to our knowledge. Issues with adherence of cART could allow for viral replication and promote chronic inflammation, which may drive frailty, potentially compounded by undertreatment of other medical comorbidities through forgetting medications for NICMs, medical appointments or other important health monitoring tasks or interventions. Broader issues around PM mistakes and undertaking effective self-care or broader physical and social participation may perpetuate frailty.

An alternative explanation for the association between greater PM complaints and frailty and the apparent grouping of less frail (robust and prefrail A) and more frail (prefrail B and frail) by lower and higher PRMQ scores respectively may be

its association with fatigue which was demonstrated to be the strongest predictor of PM complaints in those with HIV in work by Woods et al. [577]. Fatigue is common in HIV and may be characterised by the exhaustion criterion of the frailty phenotype, which was reported by 39% of our study population, increasing in prevalence with increasing frailty score, with almost three quarters of those scoring 2 (equivalent to prefrail B) complaining of exhaustion. Therefore, the increasing score on the PRMQ and PM component particularly may be driven by increasing levels of fatigue, which may precipitate memory mistakes.

We explored this potential explanation by examining the correlation (using Spearman's rank test) between PM score and proxy measures of fatigue that were used to define the exhaustion criteria of the FP. This used how many days of the week participants found everything an effort or could not get going; both of which were moderately correlated with PM score with $\rho=0.42$ ($p<0.001$) and $\rho=0.41$ ($p<0.001$) respectively. A moderate association with PM score was also seen using the energy domain of the SF-12, $\rho=-0.40$ ($p<0.001$). Fatigue may therefore be responsible for some of the poorer performance seen in PM but is unlikely to fully explain the association with frailty in our cohort.

Simple reaction time (SRT):

There was a significant increase in the median reaction time as frailty state increased across the four frailty groupings and it was the only objective test of cognition that predicted frailty in multivariable analysis with a 50millisecond response time increase associated with a 49% increased odds of frailty ($p=0.026$). This relationship was stronger after controlling for negative confounding effect of age, sex, number of comorbidities and HADS score suggesting a potentially important independent relationship between the two whilst accepting that residual confounding may exist, such as educational attainment, global cognitive score, social class, or lifestyle risk behaviours (smoking, alcohol and recreational drug use).

Slow reaction time/processing speed is one of the most consistently reported cognitive deficits in PLWH [537,553,562,581–584]. In a US study of 186 suboptimally treated PLWH, Fellows et al. showed processing speed, as assessed by three NP tests including the TMT-part A, to be significantly associated with age, current

depression, reading ability and motor dysfunction, mediating their relationships with memory and executive function. They suggest that changes in processing speed represents a primary cognitive deficit in HIV-related NCI, which may be due to the diffuse nature of HIV-related neuropathology and predilection for white matter tracts and the basal ganglia [582]. In controlled studies, HIV has been associated with slower SRT compared to negative controls [583,585], and in PLWH it has been associated with older age [583,586], poorer self-reported physical health [586] and lower nadir CD4 count [583].

Potentially therefore, reaction time deficit may be an early change in the NCI associated with HIV. In our cohort, that is not overtly symptomatic for cognitive complaints, it may represent the predominate early index of developing frailty. Specifically, we have demonstrated an independent relationship between slower processing speed and frailty, which has also been demonstrated in frail older non-demented adults in the UK using both a modified FP and a FI, though here the relationship with FP was ameliorated once MMSE score was controlled for [587]. In adults aged over 50 enrolled to the Irish Longitudinal Study on Ageing those with frailty and prefrailty performed significantly worse on all cognitive domains except processing speed [588]. In the current study, we also failed to see a processing speed relationship with the TMT-part A in multivariable analysis. This may have been due to the way we have treated the variable (i.e. by assessing the effect on 1-second increments in TMT-part A on frailty) or because we did not see a large difference in time to complete the task between frail and non-frail groups (4.7 seconds).

Overall, frail individuals took significantly longer to complete the TMT-part A test (4.7 seconds, p=0.019), further reflecting evidence of processing speed and psychomotor slowing; and longer to complete the TMT-part B (14.9 seconds, p=0.004). The composite ratio score of B/A reflects higher executive dysfunction, testing set switching and cognitive flexibility, described by removing the effect of processing speed; this did not differ by frailty status. Time to complete each part of the TMT sequentially increased with increasing frailty state with significant difference demonstrated across the four groups but again not for the ratio score, which may suggest that in this cohort processing speed is more impaired than

executive dysfunction, supporting the reaction time findings and consistent with HIV-related cognitive change. Verbal fluency as assessed by the COWAT was significantly lower in frail individuals in two and four group analyses but overall mean-word count differences were small.

The median MoCA score indicating a global cognitive performance was significantly lower in those with frailty though the actual difference was 0.5 points, with a small but significant decline in score seen over the four frailty groups. Taking a cut-off <26 to indicate cognitive impairment there was a significantly higher proportion meeting this criterion in the frail group (35.4 versus 18.5%, p=0.011), which would represent those with cognitive frailty and is equivalent to 6.7% of the cohort overall. The MoCA has the advantage of testing eight cognitive domains encompassing both cortical and subcortical facets as well as being more sensitive at detecting mild cognitive impairment. However, on comparison with NP testing it lacks the sensitivity to accurately diagnose HAND, though it could be employed as an initial screening tool [241,243,589–591], and has been advocated for use in assessing cognitive frailty alongside a test of processing speed [526].

The role of prefrailty

As hypothesised, cognitive factors did in the main worsen as frailty increased but did not cluster in lesser and higher frailty groupings as seen for the psychosocial factors. Only the PRMQ, in total, PM and RM scores, showed the same relationship with the four frailty categories, though there was no statistical difference seen between robust and prefrail A groups or between prefrail B and frail groups. In the objective tests of cognitive function, prefrail groups were in the main like each other, but overall we observed more gradual changes in cognitive function across the frailty categories.

Frailty, NCI and the potential role of cognitive reserve

The fact that we saw consistent trends for worse cognitive performance on all tested domains in most of the two and four frailty groupings suggests that frailty is associated with NCI. In this cohort, without any neurological data, we are unable to speculate as to whether this may be due to an accumulation in either

HIV or non-HIV related neuropathology reaching the threshold of brain reserve, particularly as cognitive slowing can be the result of many CNS pathologies.

We did not take any questionnaire measure of cognitive reserve, which is thought necessary to withstand the cognitive impact of these neuropathological changes, but our cohort was well-matched on premorbid IQ, sometimes used as a proxy measure of cognitive reserve. The nature of frailty is that it represents a predominantly progressive state in which multiple systems decline with the ultimate effect of functional decline and adverse outcomes. The brain and cognitive ability are likely to be experiencing the same frailty triggers as any other organ system, such as systemic inflammation, which may induce CNS dysfunction. This may drive some of the pathophysiological changes of frailty such as reduced stimulation of muscle fibres contributing to sarcopenia, as well as the presence of neurological signs particularly weakness, gait issue and psychomotor slowing in the absence of proven neurological disease, which could easily contribute to the phenotypic criteria of frailty [592]. Therefore, cognitive reserve may decline in parallel with functional reserve, which would more likely be observed as a gradual deterioration in cognitive function across frailty groups rather than discrete cognitive profiles in those on the low and high risk ends of the frailty spectrum as seen with psychosocial factors.

Lower cognitive reserve, defined using years in education, occupational attainment and premorbid intelligence, has been shown to be associated with significantly greater deficits across many cognitive domains in an asymptomatic cohort of PLWH with no similar association seen in seronegative controls [567]. Though there was no difference in baseline estimations of IQ amongst our frail group, those with frailty had less years in education (11 versus 13, $p=0.019$) and were significantly less likely to be in work (6.3 versus 43.9%, $p<0.001$) compared to non-frail individuals. If the manifestations of NCI are secondary to lower cognitive reserve this is important as although cognitive reserve is heavily influenced by early-life events it is thought to be dynamic with potential to boost reserve through physical activity, mental pursuits and educational opportunities [593].

Another explanation for the association between frailty and poorer cognitive performance in this HIV-positive cohort may be the idea of a legacy event. Heaton et al. suggested that a period of advanced immunosuppression, defined by a low nadir CD4 may leave an long-term legacy, whereby negative physiological pathways may have been triggered or irreversible structural damage made [544]. Though this was described in the context of NCI this could equally be happening to pathways involved in frailty, where low CD4 count has been the most consistent associated HIV-factor [10]. Supporting this, we have already demonstrated that in this cohort frail individuals had a significantly lower nadir CD4 count compared to those without frailty (117 versus 180, p=0.027), although the median nadir CD4 in both groups lies below 200cells/mm^3, which was the biggest HIV-related predicted of NCI in the studies described earlier. It will therefore be interesting to track the natural history of NCI in the era of universal cART prescription irrespective of CD4 count, where such nadir values can hopefully be avoided.

An alternative explanation may be that those with higher cognitive performance have greater cognitive resources to function in effectively in everyday life. This may include more effective use of healthcare resources; greater engagement with treatments and positive lifestyle changes; as well as capacity to mobilise better coping strategies and remain resilient in the face of stressors, thus avoiding frailty [594]

Strengths and limitations

The low levels of missing data are a strength and increase our confidence in the validity of our findings. We utilised standard tests of neurocognitive function performed by the same observer, reducing inter-observer variability in scoring. However, these tests were all performed in their English language form, which may have disadvantaged some participants. The fact that baseline IQ was the same for both groups reduce the likelihood that any difference in premorbid intelligence is driving the cognitive disparity seen between frail and non-frail individuals. Lastly, the testing of several cognitive domains provides strength to the relationship between cognitive factors and frailty in PLWH.

Though we tested a number of cognitive domains, we did not test the minimum five required to formally assess NCI in HIV using the Frascati criteria. Therefore, we are unable comment on the prevalence of HAND diagnoses in this cohort. Additionally, we have not compared our data to demographically comparable normative data to assess whether performance lay outside of population norms, or to make judgements about clinically relevant differences between the frailty groups. Additionally, we did not include an enquiry as to whether participants deemed themselves to have cognitive issues, therefore we cannot assess these cognitive scores in the context of symptoms.

We are also unable to differentiate between cognitive impairment that may be secondary to HIV or that which could be attributed to cognitive decline related to normal ageing or frailty (i.e. cognitive frailty), or indeed whether a combination may be at play. There may of course be an interaction between frailty and HIV in terms of risk of NCI or HIV and NCI and the risk of frailty, in that those with a combination of these may be at the highest risk of either outcome and therefore reflect the most vulnerable in the ageing HIV population. Well controlled longitudinal studies are needed to test for this possibility as it may help identify those who should be targeted for screening.

Once again the cross-sectional nature of the study limits any discussion on causality or firm conclusions about direction of association. As described it is possible that the physical and cognitive processes are occurring in parallel, but also that CNS dysfunction may impact on the physical frailty phenotype. Conversely, weakness and slow walking speed have been associated with incident mild cognitive impairment over a 12-year follow-up period [505]. Therefore, a bidirectional relationship is likely, with the possibility of an asymptomatic prodromal period, particularly regarding cognition [595].

Additionally, we can only comment on current cognitive function in relation to frailty status rather than the cognitive profile at the time of frailty development. This is particularly relevant as the natural history of HAND in well-treated cohorts is unclear with some describing a dynamic state with fluctuations in cognition and others observing stability or progressive decline; such variability is atypical for other neurodegenerative disorders [541,550,553,596].Therefore, longitudinal studies

are needed to clarify the relationship between frailty and HAND; and to address whether the natural history of cognitive change in frailty is of parallel progression or whether there may the possibility of physical predominant or cognitive predominant frailty and whether precipitants vary between them.

Multivariable analysis once again employed the same four variable model generated in line with core predictors from past research. Though age, sex, comorbidity and particularly mood disorder have been associated with NCI there is a risk of residual confounding particularly with respect to education, and other socioeconomic factors. These have been shown in well-treated adults with HIV to predict performance in NP testing in all domains except motor control, and are associated with severity of HAND [597].

6.2.5 Conclusion

We have demonstrated that frail individuals with HIV report greater everyday memory mistakes and exhibit poorer performance on tests of processing speed, psychomotor activity, executive function, verbal fluency and global cognition. Deficits of prospective memory and cognitive slowing predict frailty. Those ageing with HIV are at risk of NCI due to the competing effects of chronic HIV and its untreated and treated history, NICMs and the natural ageing process.

Cognitive reserve or indeed the presence of cognitive frailty may explain some of the differential neurocognitive outcomes experienced by individuals exposed to the same neurological threat posed by chronic HIV infection. One protective strategy may be the prevention of low nadir CD4 to avoid the legacy event of advanced immunosuppression that may start an insidious process of neurodegeneration through earlier diagnosis and cART therapy. The relationship between HIV, cognitive impairment and frailty trajectories remains unclear and would benefit from longitudinal evaluation to identify key predictors or prodromal states that may be targets for screening and intervention.

6.3 Chapter summary

Over the course of this chapter we have demonstrated that in individuals ageing with HIV, frailty and increasing frailty states are associated with cognitive dysfunction, poorer psychological outlook, smaller social networks and poorer

HRQoL. This stresses the importance of taking a biopsychosocial approach to frailty in HIV rather than focussing on the biomedical issues, which tends to predominate, particularly when a broadly physical model of frailty is used, such as the frailty phenotype.

Effective psychosocial resources of greater PIL, grit, and social support appeared to delineate low and high frailty risk groups and may protect individuals from progression to higher frailty states. The same was not seen for objective cognitive tests with performance declining as frailty increased, with slow processing speed the largest cognitive predictor of frailty.

Though we have not compared the data directly, the likelihood is that cognitive and psychosocial factors interact in the setting of frailty and HIV. For example, grittier individuals, through their determination to achieve and resilience to obstacles, may have higher cognitive reserve. A higher PIL may be associated with positive health behaviours that promote successful global and cognitive ageing. Social interaction may boost mental health, encourage cognitive and physical activity and provide a support network that can be mobilised at time of need. Being cognitively robust is essential if one is to be able to call on external resources and utilise these strategies effectively, maintain social relationships, engage proactively with healthcare and lifestyle modification, and retain autonomy and control over everyday functioning.

PLWH face many additional practical, mental, and physical stressors that accompany the diagnosis and living with an incurable chronic infection as well as those encountered through the course of usual ageing. Therefore, having cognitive reserve, robust psychological traits of well-being and resilience and being well supported socially may buffer against these stress events which unchecked may perpetuate changes in health status and potentially lead to frailty.

These associations between cognitive and psychosocial factors potentially represent targets for intervention, which would aim to boost reserve within individuals. Various studies have investigated potential interventions to promote cognitive functioning and reserve, successful ageing, psychological coping and resilience, and frailty prevention directly. Intervention studies have often

concentrated on cognitive training and rehabilitation [573,598–600] and/or physical activity and active lifestyle interventions [397,399,571,572], and have shown these targets to be amenable and feasible. However, studies are often small scale, lacking in long-term outcomes and engagement strategies, and questions over effective dose and duration of any intervention remain [571]. Additionally, most studies have focussed on single modality interventions, which may be effective on individual target domains but to achieve broader effects across psychosocial, physical and cognitive functioning, multidimensional interventions encompassing cognitive rehabilitation, mental health and well-being, resilience, social skills, and physical activity are likely to needed.

Longitudinal studies are needed to explore many important unanswered questions including whether cognitive and psychological state at baseline, measured in terms of cognitive reserve, robustness and psychological resilience influence HIV and ageing trajectories and longer-term outcomes such as frailty and NCI. Prospective approaches would allow one to assess the influence of such facets at the time of frailty development or frailty transition to delineate predictors and protective factors as opposed to cognitive and particularly psychosocial responses to frailty. This way, key targets for intervention as discussed above can be refined and tested. A life-span approach to this evaluation including different generations of HIV cohorts ageing with HIV will allow us to track how trajectories may vary as treatments and guidance change over time.

We cannot answer the question as to whether these parameters should be included into actual frailty tools as we have not looked at the predictive ability of the FP for adverse frailty outcomes in this cohort. Though it would be useful to examine frailty in PLWH using a multidimensional frailty tool, until we can better delineate the contributions of HIV and non-HIV factors to psychological and cognitive sequalae we risk over inflating both the prevalence and role of frailty. Additionally, in non-HIV settings there was no improvement in prediction of disability, HRQoL or hospital admission when cognitive, and psychosocial domains were added to physical frailty markers [458]

Our findings are important as they indicate that frailer individuals are experiencing negative cognitive and psychosocial factors, and despite good HIV-treatment are experiencing poorer HRQoL. These factors may have wide reaching implications in terms of current and future health and health service provision. Frailty may represent a means of identifying those at risk of cognitive impairment, functional decline and social isolation and its presence should prompt enquiry into memory and psychosocial concerns.

Chapter 7 – Study conclusions and future directions

7.1 Summary of findings

We have presented the first systematic review of frailty in PLWH as defined using the Fried frailty phenotype or variant thereof. This demonstrated that frailty prevalence ranged from 2.9-28% depending upon study population. Study cohorts were heterogeneous regarding among other things, age, gender and ethnic mix, geographical location, and period on the HIV timeline that was reported upon, which influenced HIV factors including duration, immune status and treatment experience. Additionally, there was diversity as to how the FP criteria were defined with the combination of these leading to a degree of heterogeneity that prohibited meta-analysis. The review highlighted that HIV serostatus, age and comorbid disease, particularly depression, were associated with frailty in PLWH. HIV factors including CD4 count, VL and AIDS diagnosis were also associated with frailty, with the greatest increase in risk seen for low current CD4 count. This review of the literature importantly described frailty prevalence in detail in those with HIV, which exceeds that seen in HIV-negative cohorts of equivalent age, and thus appears to be occurring earlier in the life course than may be anticipated based on population studies of frailty in HIV-negative groups. It was also successful in outlining those factors that may be conferring an additional risk for frailty in those with HIV, which appear to be shifting away from HIV-related factors in more treatment experienced cohorts [10,190].

The cross-sectional study reported upon in this thesis is important as it presents the some of the first UK data on frailty in specifically older people with HIV. We have shown frailty prevalence to be high at 19% based on a prospectively applied frailty phenotype containing objective grip strength and walking speed parameters. The prevalence places the cohort towards the higher end of the range reported in the literature to date, though the upper and lower confidence intervals of 14.6 and 24.3% fall entirely within this range lending weight to the validity of this result. This prevalence is higher than hypothesised given that most individuals will have been treated wholly or predominantly in a system where there is free universal access to healthcare, which one might have anticipated to

confer a better health status and as such less frailty. The higher prevalence may be a product of the older median age of the cohort at almost 60, making the population one of the oldest reported upon. However, given that 50% were under 60, this prevalence is supportive of the premature occurrence of frailty, though we had no representative control group to compare against. Alternatively, the high prevalence may be in part due to the way the frailty phenotype was adapted through use of single questions rather than more objective scales to rate low physical activity and to a lesser extent, exhaustion, thus potentially inflating the prevalence of these components and pushing individuals into higher frailty categories.

Irrespectively, the fact that potentially 20% of PLWH over 50 could be frail has significant consequences for HIV services as these individuals may be higher users of healthcare, and be at risk of hospitalisation and functional decline. Consequentially, they may present to their HIV clinicians more frequently with issues that could be considered to represent frailty syndromes such as falls, mobility problems and functional difficulties, all of which were common in this cohort predominantly made up of middle-aged individuals.

We examined the association between frailty and a broad range of potentially related factors based on the ageing and HIV literature. We demonstrated that non-HIV factors showed greater association with frailty than HIV factors, which were not associated with being frail in either univariate or multivariable analysis. Although we did not show an association with HIV-factors and frailty, it is possible that HIV may be driving some of the processes leading to frailty, such as chronic inflammation. These may occur earlier in the frailty pathway at times of more marked immunosuppression, akin to the ‘legacy event’ described in the pathogenesis of HAND that we are not capturing, or frailty is conferred via mechanisms not illustrated by the included HIV parameters. However, increasing numbers of comorbidity and increasing HADS scores reflecting mood symptoms were associated with a 58% and 17% increase in the odds of frailty respectively. We did not demonstrate a higher age amongst those with frailty or an increased burden of frailty with increasing age-group. After controlling for HADS score and depression however, age was associated with increased odds of frailty,

suggesting that comorbidity and mood disorder may be particularly associated with frailty in a broadly middle-aged cohort, but in their absence, age remains a significant correlate. Therefore, optimisation of non-infectious comorbidities and actively seeking out and managing mood disorder may reduce frailty risk and shift frailty towards older ages as is seen in HIV-negative cohorts; though this would need to be corroborated in larger controlled studies.

We have shown that low muscle mass is common in PLWH at around 50% irrespective of frailty status, with 1 in 5 meeting a standardised definition of sarcopenia based on objective DXA scanning. The effect of HIV on muscle and sarcopenia has largely been neglected in the literature, yet we have shown that sarcopenia and increasing degrees of sarcopenia compared to normal muscle mass were associated with frailty. Sarcopenia and frailty are not mutually exclusive, which was shown in the DXA subgroup where 55% of those with frailty were not sarcopenic and 36% of those with sarcopenia were not frail. However, it has been suggested that sarcopenia is a pathophysiological precursor to frailty and as such warrants further investigation, particularly given the high proportion with low muscle mass overall [592]. Sarcopenia may represent an intermediary step where some of the measured parameters, particularly those factors explored in chapter 5 may be playing a role, including nutrition, physical activity and chronic inflammation, and the relationship between these and sarcopenia should be examined.

Our approach is novel in that we chose to explore potential frailty predictors in an HIV-positive cohort from the perspective of a geriatrician, whilst incorporating key HIV factors drawn from our systematic review and the broader literature. We selected parameters from a number of domains that would be covered in a Comprehensive Geriatric Assessment, which has been utilised as both a means of identifying frailty [601,602] and a recommended holistic assessment intervention following the potential identification of frailty [411]. This approach led to a biopsychosocial (and cognitive) exploration of frailty in the same cohort, which we have not seen presented elsewhere. We have identified a number of additional potentially important correlates with frailty including financial insecurity, smoking, medical comorbidity and number of non-antiretroviral medications,

chronic pain, sarcopenia, low physical activity, and elevated IL-6. These factors are broadly consistent with the existing literature and we have described the potential pathways through which they could contribute to frailty, particularly to Fried's theorised cycle of frailty. Though we cannot imply direction of association or causality, these findings support that frailty in an individual with HIV corresponds to the notion of frailty that has been widely described in older (>65 years) HIV-negative cohorts. Further to this, the correlated factors identified mirror those that have been suggested and trialled as practical targets for intervention within health and social care settings. These include comorbidity management, rationalisation of non-antiretroviral medications, tackling lifestyle risk factors, especially promoting smoking cessation, physical exercise and nutrition [105,140].

Our exploration of psychosocial and cognitive factors in relation to frailty in HIV represents novel data. We found that frail individuals were more likely to have smaller social networks, be socially isolated, report lower purpose in life and have less gritty personalities; as well as performing worse on all measured cognitive domains. However, in multivariable analysis only slow processing speed and greater prospective memory complaints retained an association with frailty, with a trend toward reduced frailty as purpose in life increased (p=0.05). We had hypothesised that positive psychological traits and higher cognitive function might protect against higher frailty states, delineating lower and higher frailty risk groups based on phenotype score, with prefrail individuals behaving more like robust or frail individuals depending on whether they score on one or two frailty criteria respectively. We demonstrated this to be the case for the positive traits of purpose in life and grit, but not social network size. This suggests that positive psychology may provide a buffer to physiological and health stressors that may help to prevent transition to frailer states. The same was not seen for cognition however, suggesting that cognitive function may decline gradually as frailty state worsens, in keeping with multisystem decline.

Overall, we have demonstrated in a well-treated, older HIV-positive cohort engaged in HIV care that frailty is common; as are other age-related problems including sarcopenia, comorbidity, falls and mobility issues and difficulties with

ADLs. Additionally, we have shown that frailty is not purely correlated with biomedical predictors and that it is important to view frailty in light of adverse socioeconomic, psychosocial and cognitive factors. Frailty represents a negative ageing trajectory and though we cannot say with certainty that the factors negatively associated with frailty would be positively associated with robustness or that robustness is equivalent to successful ageing, however these traits should be corroborated in larger controlled studies. From these, potential interventional targets could be explored to reduce, prevent or reverse frailty in those at risk or maintain more successful ageing trajectories in robust individuals. These interventions are likely to be multifactorial, incorporating health and well-being strands over pharmacotherapy.

7.2 Study limitations

The study has a number of limitations that have been outlined throughout the chapters and therefore the data presented and the inferences drawn should be viewed in the context of these. Study sampling was not random but based upon consecutive invitation of all potentially eligible persons when they were seen within their HIV service over a one year period. During this timeframe, we anticipated that all potential participants would have been offered information regarding the study at least once to minimise sampling bias. However, it is possible that those perceived to have frailty by their clinician or those more concerned about issues of ageing personally may have preferentially enrolled to the study thus potentially overestimating frailty. This may be compounded if fitter, more robust individuals opted not to participate. Conversely, those with the greatest health and/or functional problems within the cohort may have elected not to participate due to the perceived or actual burdens of the study or physical inability, which may have resulted in an underestimation of frailty. Though, the former hypothetical scenario is more likely. However, we were unable to compare those enrolled to those not interested in engaging in the study but anonymised data from the Brighton recruitment centre of those who showed interest in but did not enter the study were similar with respect to demographics and HIV factors, which if reflective of the whole clinic population would suggest we are unlikely to have greatly over-estimated frailty.

The inclusion and exclusion criteria were designed to be as inclusive of the current ageing cohort as possible and therefore we did not exclude individuals based on specific comorbidities, as was done in the original Cardiovascular Health Study from which the frailty phenotype was operationalised [9]. Here they excluded conditions such as Parkinson's disease and formally diagnosed dementias as they felt the expression of the phenotypic criteria of frailty could be a consequence of these diseases rather than the multisystem decline thought to typify frailty. We did not take this approach and although we did not have any participants with those specific conditions it is possible that some manifestations of frailty may have been driven by one specific comorbidity. Additionally, though we deferred entry to the study for those in whom a transient frailty state may be present due to potential deconditioning from an intercurrent acute illness, there is no actual evidence on timing of functional recovery so in choosing an arbitrary deferment of six weeks we may have still been capturing 'acute' rather than a 'chronic' or true frailty state. However, the impact of these is likely to be small and the persistence of a frail state and broader frailty dynamics will be explored using prospective data.

We did not reach our planned recruitment target and there was under recruitment of women and those of black ethnicity to match the UK older adult HIV-positive population. This resulted in a study cohort that is predominantly white male, mostly identifying as MSM, which though representative of the coastal Sussex HIV demographic may limit generalisability of results to the whole UK HIV-positive population, particularly women; or indeed to wider settings such as those with lower cART uptake or differing healthcare service structures, including more resource limited settings.

Though comparable to others, the cohort is relatively small and as mentioned we failed to achieve our targeted sample size of 300 participants. Consequently, though the prevalence of frailty was considerable at almost one in five participants the relative number of frail individuals was still low at 48. The small sample size has limited the precision of effect size estimates, with wide confidence intervals seen in places, especially in the context of overall frailty prevalence where our precision-based sampling strategy had aimed for a range of +/-3% had we fully

recruited. However, the greater prevalence has provided larger numbers for comparison than we would have seen with the predicted prevalence of 10% in a cohort of 300, with the greater number of outcomes potentially strengthening the analyses.

The number of outcomes seen (i.e. frail individuals, n=48) did limit the number of parameters that could be factored into the logistic regression model, restricting it to the four core parameters of age, sex, HADS score and number of comorbidities. It is likely therefore that there is residual confounding that has not been accounted for. The same could be said for multi-collinearity, though we did test for this and excluded closely related variables. The model did not afford room to examine for any interactions within these data. Lastly, testing the association with frailty for such a large number of variables risks increasing type I error so that some findings may be secondary to chance rather than true relationship.

This observational study presents cross-sectional data and as such we cannot make any assumption as to causality or the direction of any of the presented associations with frailty. However, we have presented data trends and utilised existing literature to illustrate and support where relationships are likely to be predictive or protective for frailty and explored where potential bidirectional connections may exist, such as in the case of frailty and depression. Importantly, the study lacks an HIV-negative control group and thus we cannot truly say that frailty is more or less prevalent, or has different predictor variables in those with and without HIV. However, we are cognizant of this limitation and have referred to how our results compare to both controlled studies of frailty and HIV and to frailty investigations in HIV-negative cohorts throughout.

7.3 Unanswered questions and future directions.

Demographic considerations

It is possible that ageing trajectories may alter as the HIV epidemic continues to mature. The current HIV-patient population is made up of differing cohorts depending upon when they were diagnosed on the HIV timeline. Thus, current HIV and ageing research will encompass those diagnosed early in the epidemic in a time of no effective antiretroviral therapy and higher rates of advanced

immunosuppression and AIDS defining events. The survivors of this period and those diagnosed in the mid-1990s may have been exposed to first generation antiretrovirals that often-had greater toxicities and longer-term adverse effects. These may have resulted in resistance, drug changes and exposure to greater numbers of different antiretrovirals. Additionally, treatment guidance has evolved with those diagnosed earlier treated in line with guidance that promoted later cART initiation, therefore were potentially exposed to lower CD4 counts, especially <350, which has been associated with frailty as discussed. There are also those diagnosed in a time of proactive testing protocols, and effective cART with ever reducing drug toxicities and less burdensome regimens that may facilitate adherence. However, those aged over 50 remain at risk of late diagnosis, which is associated with greater immunosuppression and worse outcomes [48,603]. Those individuals with timely diagnosis, commenced immediately on an adherent and successful modern cART regime may follow ageing trajectories more akin to or the same as usual ageing. Therefore, it will be important to track changing ageing demographic profiles as the different 'generations' of PLWH age or evaluating stratification by these subgroups, with appropriate sample size requirements taken into consideration.

Current research into HIV and ageing centres around the historical older age cut-off at 50, so research continues to focus on what would be considered middle-age in non-HIV settings. Though it may be important to try and delineate whether premature or accelerated ageing is occurring in HIV, we must examine the emerging issues affecting those in traditional aged categories (>65) given the projected normalisation of life expectancy. It will be important to describe the ageing profiles of those in their 60s, 70s and beyond to know whether there is any excess of age-related problems (accentuated ageing) in those with HIV, particularly frailty at these higher ages. Currently data on traditional age-related pathologies including stroke, and neurodegenerative disorders such as Parkinson's disease and non-HIV related dementias is lacking. Additionally, in those reaching very old age we should investigate whether any HIV-related factors influence long-term survival.

We must acknowledge that the data and supporting literature presented in this thesis predominantly applies to high resource countries with higher usage of cART and more wide scale access to comprehensive healthcare systems. Therefore, the findings may not apply to more resource limited settings where issues of ageing in the context of HIV may be a lesser healthcare priority compared to cART roll-out, OI treatment, and preventative strategies. However, our findings broadly concurred with those of Pathai et al. in their South African study [181] and there is a growing literature around issues of ageing in these settings. This may increase in importance as the UNAIDS report of 2013 clearly demonstrated global ageing of HIV cohorts [604]. As the greatest burden of HIV falls on low- and middle-income countries, particularly in sub Saharan Africa, this will become a growing challenge for health services, where expertise in geriatric medicine is often lacking [605–608].

Unanswered questions

We defined frailty using one method in this study and although the frailty phenotype has been the most utilised tool in both HIV and non-HIV settings [10,11,109], whether it represents the best tool in HIV is unknown as no comparative studies exist. Even with the phenotype, the optimal method to operationalise the five criteria in HIV has not been assessed, with authors, including ourselves using cut-offs for objective measures based on the Cardiovascular Health Study population, which is unlikely representative of current older adults with HIV. There are a broad range of frailty tools and an alternative may define frailty in HIV better than the phenotype, particularly those that include mood, psychosocial and cognitive domains that we have shown to be important in this cohort. It is also important to consider what will be useful in the clinical setting as the inclusion of grip strength and walking speed may make the phenotype impractical in routine HIV care. We plan to analyse the performance of number of frailty tools compared to the FP in this cohort.

One of the major limitations of this and many of the frailty studies in PLWH is their cross-sectional design. This constrains our findings in terms of their validity, generalisability and biological plausibility. Therefore, it will be vital for our findings, particularly the higher prevalence rate, to be corroborated in a larger controlled

cohort to assess whether associations hold. Such a cohort may be the currently running UK-based Pharmacokinetic and clinical observation in people over 50 (POPPY) study, which has enrolled HIV-positive individuals aged older and younger than 50 alongside an HIV-negative group aged over 50 drawn from sexual health clinics to provide a demographically and behaviourally representative control.

There is little longitudinal data on frailty in PLWH and therefore the natural history remains largely unknown. It will be important to know if frailty trajectories in those with HIV align with that seen in HIV-negative older adults. Primarily frailty has been found to be progressive, but in some it can be dynamic with individuals moving in and out of frailty categories or regressing to more robust states [138,139]. Indeed, fluctuations in frailty status were seen in the MACS longitudinal study in men where frailty was assessed 6-monthly [176]. If frailty is highly fluctuant in PLWH then it may not represent a useful construct in terms of clinical risk prediction. Furthermore, though the assumption is that frailty in younger individuals with HIV represents the same process seen in those without; we do not know whether frailty in HIV is associated with the same adverse outcomes seen in frail HIV-negative individuals. Prospective studies assessing baseline frailty and subsequent outcomes of mortality, hospitalisation, functional decline and falls in PLWH are lacking. We have demonstrated increased falls rate and functional disability (ADLs) as well as lower HRQoL in frail individuals in this cohort based on cross-sectional data. We will be able to add data regarding these questions using a second frailty assessment and adverse outcome reporting undertaken at one-year follow-up.

Ultimately, good quality prospective longitudinal studies with appropriate control groups that embed frailty assessment and core frailty predictors/protective factors are needed. This needs to take a ‘lifespan’ approach in that frailty is assessed at baseline in all participants, irrespective of age, so that we can ascertain frailty prevalence and incidence by age group and assess frailty dynamics defined by transitions in frailty status. As well as tracking the natural history, to answer questions such as: at what age do we see people becoming frail (and/or sarcopenic) in HIV? What factors are present around time of frailty development?

What are the potential pathophysiological pathways? Is normal ageing physiology altered in PLWH? and what are the adverse outcomes, if any, associated with frailty in PLWH?

Obviously, such studies are costly, and hard to establish. Therefore, we advocate the continued inclusion of prospectively collected, objective frailty parameters within established cohorts such as MACS, VACS and WHIS. However, these are US-based, and have a different demographic mix to the UK HIV-positive population. We hope that more recently established cohorts such as POPPY and ours here in the UK and AGEhIV in The Netherlands may be able to have some element of medium- to long-term follow-up to address the above goals. An alternative approach may be to lobby for ageing parameters to be incorporated into registry data on a periodic basis. Additionally, attempting to standardise the frailty assessment and outcome measures used across studies would be beneficial in reducing heterogeneity, and making data pooling and direct comparisons between cohorts easier. The lack of definitive diagnostic criteria for frailty does limit this however.

The future

Taking the work presented in this thesis forward, we aim to investigate the role of alternative frailty assessment tools; and analyse data from year one follow-up visits to assess frailty dynamics, and the relationship between baseline frailty status and known outcomes of frailty. Mood disorder and non-infectious comorbidities represent candidate drivers of frailty, therefore these warrant further investigation, particularly regarding how optimally they are being identified and managed across HIV services and primary care. The potential involvement in primary care may allow us to explore the value of the electronic frailty index, which has been developed using existing primary care clinical database information. This may be a mechanism of assessing frailty across the wider cohort, increasing power for multivariable modelling and providing a continuous value that could be monitored over time.

What does this mean for clinicians?

Frailty is common in older adults using HIV services in Sussex at almost 20%, with high reported levels of falls, mobility impairment, and functional difficulties. This is coupled with high rates of non-infectious comorbidity and symptoms of mood disorder, which appear more important drivers of frailty compared to chronological age or HIV-factors.

This constellation of problems makes this group of service users medically complex, with the potential for increased use of HIV-services for primarily age-related issues. If and how frailty should be embedded into HIV-services remains to be seen, and certainly there is insufficient evidence to suggest routine frailty screening of PLWH. This echoes the opinion of the British Geriatrics Society, who have produced guidance on when and how to assess frailty in wider clinical settings for older adults [411]. Ultimately, HIV-physicians will require an awareness of age-related issues and enquire as to mood, cognition, mobility, falls and functional decline. There is an appetite for greater guidance on monitoring older adults with HIV amongst HIV physicians [609]. In time, clinical pathways that utilises the patient's GP, a multi-disciplinary team and/or geriatricians may be encouraged to allow referral for formal assessment. This will rely on mutual education on age in the context or HIV and vice versa to upskill respective specialty clinicians to the potential complexity of this cohort.

Importantly, the patient voice is missing from this study as there was no included qualitative work. It will be of interest to capture the opinion of service users regarding some of the terminology of ageing, particularly frailty. A study in adults over 70 conducted by Age UK and the British Geriatrics Society around the language of ageing showed that most participants did not identify with 'frail' or 'frailty'. They felt these had negative connotations, preferring to describe ageing in terms of functionality [610]. However, an understanding of frailty concepts at least will be critical in empowering PLWH to recognise and report troublesome age-related issues; acknowledge that they are not necessarily irreversible; facilitate engagement with 'ageing services' and the broader MDT, and hopefully in time with frailty intervention trials.

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Appendix 1: Systematic review publication

Systematic Review of Prevalence and Predictors of Frailty in Individuals with Human Immunodeficiency Virus

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OBJECTIVES: To describe the prevalence and predictors of frailty in individuals with the human immunodeficiency virus (HIV) using systematic review methodology.

DESIGN: Review.

SETTING: Community.

PARTICIPANTS: Older adults with HIV.

MEASUREMENTS: Medline, CINAHL, EMBASE, PsychInfo, and PubMed were searched for original observational studies with populations including individuals with HIV in which frailty was assessed using the frailty phenotype or a variant thereof. Studies were examined for frailty prevalence and predictors of the syndrome in those with HIV.

RESULTS: Thirteen of 322 citations were included for full review. All demonstrated the presence of frailty in individuals with HIV, with prevalence ranging from 5% to 28.6% depending on population studied. HIV was a risk factor for frailty. Predictors of frailty included older age, comorbidities, diagnosis of acquired immunodeficiency syndrome, and low current $CD4^+$ cell count.

CONCLUSION: HIV appears to be an independent risk factor for frailty, with frailty occurring in individuals with HIV at rates comparable with older individuals without HIV. Heterogeneity in study populations and frailty assessment measures hamper accurate description of the problem. Future longitudinal work with standardized methodology is needed to describe prevalence accurately and confirm predictors. **J Am Geriatr Soc 64:1006–1014, 2016.**

Key words: HIV; frailty; prevalence; aging

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Longer survival with modern combined antiretroviral therapy (cART) alongside greater incidence of late-life acquisition of the human immunodeficiency virus (HIV) is driving an increase in the age of the HIV-positive (HIV+) cohort. HIV in older adults presents a number of challenges, including comorbidities not traditionally associated with HIV infection,[1] including falls,[2] functional impairment,[3] and frailty,[4] which are more common in older adults. Whether HIV itself or treatment toxicities cause premature or accelerated aging is subject to ongoing debate[5,6] and is considered a research priority.[7]

With an increasing number of older adults receiving HIV care, services will need to be adapted to meet their complex needs. In general, chronological age may not be the best predictor of prognosis or individual need;[8] a more-useful model for risk stratification may be the presence or absence of frailty. Frailty describes a state of vulnerability to stressor events resulting from declines in multiple physiological systems. When present, frailty is associated with adverse outcomes including falls, hospital admission, and death.[9–11] The difficulty in using frailty as a concept is the lack of consensus definition, particularly regarding how it should be measured.[12] The most widely used model in HIV+ and HIV− populations is the frailty phenotype (FP)[13] characterized by Fried and colleagues.[9] The FP comprises five criteria (weight loss, exhaustion, low physical activity, weak grip strength, slow walking speed), with frailty defined according to the presence of three or more criteria. Those with one or two are classed as prefrail and with none as robust.[9]

There is heterogeneity in HIV frailty research, with different authors using various measures and definitions of frailty, making it difficult to quantify the burden of frailty fully in the context of HIV. The objective of the current study was therefore to conduct a systematic review of the original literature pertaining to frailty prevalence and predictors in individuals with HIV using the FP as a standard model.

JAGS 64:1006–1014, 2016

0002-8614/16/$15.00

METHODS

Search Strategy

The goal was to identify observational studies assessing frailty status in individuals with HIV. A systematic electronic search was conducted using Medline, CINAHL, EMBASE, PsychInfo, and PubMed, which were searched from January 2000 to April 2014 using database-appropriate medical subject headings alongside "HIV," "human immunodeficiency virus," "acquired immunodeficiency syndrome" combined with "frail*," "reduced functional reserve," "functional impairment," "reduced physiological reserve," and "physiological vulnerability." Broad "function" terms were used to capture studies in which frailty was part of a wider functional assessment. International HIV and acquired immunodeficiency syndrome (AIDS) conference abstracts, major HIV and gerontology journals were also searched. Reference lists of relevant review articles and articles reviewed at full-text stage were screened by hand.

Eligibility Criteria

The following inclusion criteria were applied in article selection: original observational research presented; frailty defined using the Fried FP, or modified variant thereof, to allow standardization (therefore excluding studies published before its description in 2001; inclusion of data on HIV+ adults; and frailty prevalence for individuals with HIV stated, easily calculable, or obtainable from authors). Studies not meeting the above criteria were excluded. Although language was not an exclusion criterion or limit set during searches, all citations found were in English.

Study Selection

Two reviewers (TL, FC) independently conducted selection for full-text review by applying eligibility criteria to titles and abstracts. Articles deemed relevant or for which further clarification was required were retrieved for full text review. Authors were contacted when points of clarification were needed.[14–16] The reviewers independently assessed selected full-text articles, and after discussion and consensus review where needed (by MF), a list of studies for inclusion was finalized.

Quality Assessment

Study quality was evaluated with respect to bias using the Newcastle–Ottawa Scale (NOS),[17] a quality assessment tool for nonrandomized studies with scales available for different observational methodologies, which were applied according to study type. Broadly, the NOS criteria evaluate quality in the domains of selection, comparability, and outcome, awarding a designated number of stars to each study in each domain depending on whether quality markers are met. The scale was adapted for cross-sectional studies by reducing the weight allocated to validation of exposure (HIV) and outcome (frailty), to be awarded 1 rather than 2 points, making weighting comparable with that awarded for cohort and case–control scales, preventing artificially high-quality scoring of cross-sectional studies. Given the importance of statistical analysis, scoring for an appropriate approach was substituted into schemes for cohort and case–control study design types.

Data Extraction

Two of the authors (TL, FC) designed a data extraction form and independently applied it to each study. Data were extracted on study design, population characteristics, frailty definition and frailty prevalence (for HIV+ and HIV− when control groups were included), and significant frailty predictors. Data that each reviewer extracted were compared for consistency, and any disagreements were resolved by consensus or a third reviewer (MF).

Statistical Analysis

A meta-analysis of frailty prevalence was planned to generate a summary prevalence with corresponding 95% confidence intervals (CIs). Comprehensive meta-analysis software was used. A random-effects meta-analysis of the included studies presenting cross-sectional data was performed,[14,18–23] producing summary prevalence of 8.6% (95% CI = 6.5–11.3), although heterogeneity was high, with an I^2 score of 77.63, which did not fall to below 75 with sensitivity analysis when additional factors were considered, including country of origin (U.S. vs non-U.S.), ethnicity (white vs black), age (<vs ≥50), or ART use (whole cohort vs <100% use). Given that variability in prevalence is largely due to heterogeneity of the studies, it was decided not to present the findings as a meta-analysis. A funnel plot was created to assess potential publication bias (Figure 1), which owing to the limited number of studies in the review, could not provide conclusive evidence, although from the observed funnel plot, the spread of studies was more or less symmetrical, suggesting an absence of publication bias.

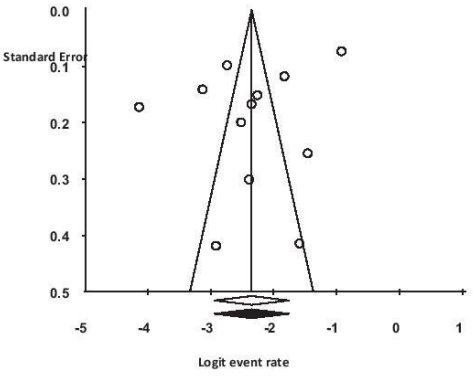

Figure 1. A funnel-plot to assess publication bias of included studies (using random effects model)

RESULTS

Search Results and Study Selection

Literature review found 322 citations: 275 from database searches and 47 from index searching of bibliographies, journals, and conference proceedings. Of these, 103 were duplications, and a further 178 were excluded after title or abstract review because of nonrelevance. Forty-one were selected for full-text review, with a further 28 exclusions due to duplicated presentation of data (n = 6), lack of frailty assessment (n = 12), frailty not defined by FP (n = 4), or absence of primary data (n = 6). Thirteen studies met full inclusion criteria. Selection and exclusions are shown in Figure 2.

Study Characteristics

Of the 13 studies selected, five were of cohort design (two prospective, three retrospective),[15,16,24–26] with four presenting data from the Multicentre AIDS Cohort Study (MACS).[16,24–26] One study used case–control design,[21] and seven were cross-sectional[18–20,22,23,27] (one nested within a prospective cohort);[14] 12 were presented in full article format and one as a conference abstract. Studies were largely urban community or university clinic based, with only one from a resource-poor setting.[21] Studies varied in size from 41 to 2,150 participants. Eleven studies were U.S. based, with the two remaining studies from Mexico and South Africa. All used a frailty assessment based on FP criteria, with the three retrospective cohort studies using a frailty-related phenotype (FRP) comprised of four rather than five criteria, with grip strength data lacking.[24–26] One study measured phenotypic criteria differently from other studies.[27] General study characteristics and description of frailty parameters are shown in Table 1.

Quality

Quality as assessed using design-specific NOS showed that, of a maximum available 9 points, there was a range from 3 to 8, with a lower-quality score assigned to the conference abstract (Table 2).

Frailty Prevalence

Prevalence was measured in two ways. When cross-sectional data were presented, prevalence was provided for individuals and ranged from 5% in the Mexican study[22] to 28.6% in the MACS cohort.[16] In the MACS articles, frailty was assessed on multiple occasions, allowing for prevalence to be calculated using total number of individuals as the denominator (based on at least one visit with frailty), ranging from 13.9% to 28.6%, and using total person visits as the denominator, which resulted in lower prevalence (5.4–12%).[16,25] Across the MACS timeline, prevalence of frailty in terms of person-visits decreased from 7.6% in 1994–95 (pre-cART era) to 4.5% in 2000–05 (post-cART era), with increases in median age from 41 to 48 and proportion of those on treatment from 42.3% to 80.2%. In the most-recent evaluation, from 2007 to 2011 (established cART era), with frailty assessed prospectively with the addition of grip strength, prevalence had risen to 12% of visits or 28.6% of individuals with at least one frailty visit, along with further increases in median age to 53.8 and in proportion receiving cART from 80.2% to 84.2%. Data were presented from the AIDS Linked to the IntraVenous Experience (ALIVE) cohort, including HIV+ and HIV− individuals with past or present intravenous drug use, in which FP was present in 12.3% of all participants and 12.4% of person visits.[15] Dividing participants according to HIV status, 14.6% of HIV+ and 11.3% of HIV− were frail (data provided by author).

Predictors of Frailty

HIV Status

Five studies included HIV− controls. The MACS cohort examined frailty before the introduction of cART,[24] when the prevalence of FRP in HIV− participants was 1.5%. In this study, for 1994 to 1996, the odds of expressing FRP,

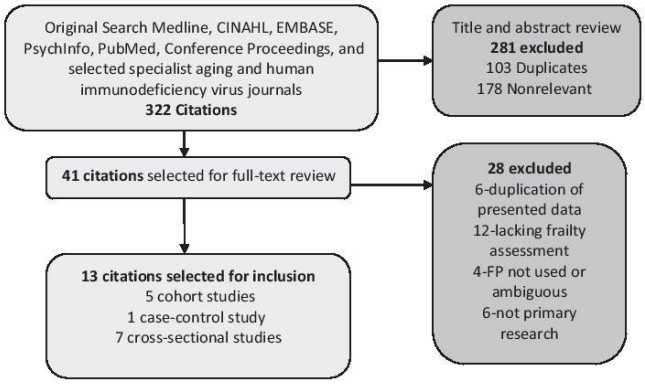

Figure 2. Flow diagram of reviewed studies.

Table 1. Characteristics of Included Studies

Author, Year (Country)	Design	Population	Age of HIV+ Participants	Male, %	Study Population, N	HIV+, n	HIV+ and Frail, %	Outcome Measure	Frailty Criteria
Althoff, 2013 (United States)[16]	Cohort	MACS Men who have sex with men aged ≥18 ± HIV Urban community Oct 2007-Sept 2011	53.8 frail, 50.5 nonfrail (median)	100	1,946	898	28.6 (12)[a]	Prospective Modified FP Frail if ≥3/5 criteria	Weakness (grip strength[b]) Slowness (4-m timed walk[b]) Self-reported weight loss Self-reported exhaustion[c] Low physical activity[d]
Desquilbet, 2007 (United States)[24]	Cohort	MACS HIV− cohort Apr 1994-Nov 2004 HIV+ cohort Apr 1994-Jan 1996	39 (median)	100	2,150	245	13.9 (7.2)[a]	Retrospective FRP Frail if ≥3/4 criteria	Self-reported slowness[e] Self-reported Self-reported exhaustion[c] Low physical activity[d]
Desquilbet, 2009 (United States)[25]	Cohort	MACS HIV+ cohort April 1994-April 2005	45 (median)	100	1,046	106	— (5.4)[a]	Retrospective FRP Frail if ≥3/4 criteria	Self-reported slowness[e] Self-reported Self-reported exhaustion[c] Low physical activity[d]
Desquilbet, 2011 (United States)[26]	Cohort	MACS HIV+ cohort initiating ART pre-2001	43 (median)	100	596	596	13.9	Retrospective FRP Frail if ≥3/4 criteria	Self-reported slowness[e] Self-reported Self-reported exhaustion[c] Low physical activity[d]
Erlandson, 2012 (United States)[18]	Cross-sectional	HIV+ aged 45–65 on ART University hospital clinic January 2009-January 2010	50.8 (median)	85	359	359	7.5	Prospective modified FP Low function (frail) if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m timed walk[g]) Self-reported weight loss Self-reported exhaustion[h] Low physical activity[d]
Greene, 2014 (United States)[23]	Cross-sectional	Community study HIV+ aged 50 on ART	57 (median)	94	142	142	8.5	Prospective FP	Fried phenotype Individual criteria not specified
Ianas, 2012 (United States)[19]	Cross-sectional	Convenience sample; HIV+ aged ≥18 ± ART University outpatient clinic May-December 2010	21–78 (range)	74	100	100	19.0	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m timed walk[g]) Self-reported weight loss Self-reported exhaustion[h] Low physical activity[d]
Onen, 2009 (United States)[20]	Cross-sectional	Convenience sample University hospital clinic HIV+ aged ≥18 ± ART June-December 2008	41.7 (mean)	71	445	445	9.0	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m timed walk[g]) Documented weight loss Self-reported exhaustion[h] Low physical activity[d]
Pathai, 2013 (South Africa)[21]	Case-control	Unselected sample aged >30 HIV+ ± ART Community treatment center HIV− controls community HIV prevention site May-Dec 2011	41.1 (mean)	27	504	248	19.4	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m timed walk[g]) Documented weight loss Self-reported exhaustion[h] Low physical activity[d]

(Continued)

Table 1 (Contd.)

Author, Year (Country)	Design	Population	Age of HIV+ Participants	Male, %	Study Population, N	HIV+, n	HIV+ and Frail, %	Outcome Measure	Frailty Criteria
Piggott, 2013 (United States)[15]	Cohort	AIDS Linked to IntraVenous Experience History intravenous drug use ± HIV Community-based cohort From July 2005	48.7 (median)	63	1,230	357	14.6	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength[f]) Slowness (4.5-m timed walk[g]) Documented weight loss Self-reported exhaustion[h] Low physical activity[d]
Sandkovsky, 2013 (United States)[27]	Cross-sectional	Pilot study Convenience sample University hospital clinic HIV+ aged 20–39 or ≥50 ± ART	20–70 (range)	71	41	41	17.1	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip >1 standard deviations below mean) Slowness (Timed Gait Test >11 seconds) Self-reported weight loss Exhaustion (Fatigue Severity Scale score >36) Low activity (POMS activity scale <2)
Terzian, 2009 (United States)[14]	Cross-sectional	Nested within Women's Interagency HIV Study Urban, community cohort of women aged ≥14 ± HIV Jan-Dec 2005	41 (median)	0	1,781	1,206	9.0	Prospective modified FP Frail if ≥3/5 criteria	Weakness (grip strength) Slowness (4-m walk time) Self-reported weight loss Self-reported exhaustion[h] Low physical activity[d]
Abstracts									
Davila-De la Llavre, 2013 (Mexico)[22]	Cross-sectional	Community study HIV+ aged ≥50 on ART	54 (mean)	80	116	116	5.0	Prospective FP	Fried phenotype Individual criteria not specified

[a]Frailty prevalence based on percentage of visits at which frailty identified.
[b]Lowest 20% for activity.
[c]Answered "yes" to "During the past 4 weeks, as a result of your physical health, have you had difficulty performing your work or other activities?"
[d]Answered "yes, limited a lot" to "Does your health now limit you in vigorous activities?"
[e]Answered "yes, limited a lot" to "Does your health now limit you walking several blocks?"
[f]Predefined cutoffs based on sex and body mass index.
[g]Predefined cutoffs based on sex and height.
[h]Response of 3–4 days per week or most of the time to "Everything I did was an effort" or "I just could not get going," on the Center for Epidemiologic Studies Depression Scale.
[i]Minnesota Leisure Time activity questionnaire.
ART = antiretroviral therapy; FP = frailty phenotype; FRP = frailty-related phenotype; MACS = Multicentre AIDS Cohort Study; HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

Table 2. Newcastle–Ottawa Scale Quality Evaluation According to Design Type

First Author, Year	Selection	Comparability	Outcome	Total
Cohort design				
Althoff, 2013[16]	3	2	3	8
Desquilbet, 2007[24]	2	2	3	7
Desquilbet, 2009[25]	2	2	3	7
Desquilbet, 2011[26]	3	2	2	7
Piggott, 2013[31]	2	2	2	6
Case–control				
Pathai, 2012[21]	2	2	3	7
Cross-sectional				
Erlandson, 2012[18]	2	2	3	7
Greene, 2014[23]	2	0	2	4
Ianas, 2012[19]	2	2	3	7
Onen, 2009[20]	3	0	3	6
Sandkovsky, 2013[27]	3	1	2	6
Terzian, 2009[14]	2	2	3	7
Abstracts (cross-sectional)				
Davilla, 2013[22]	2	0	2	4

adjusted for age, ethnicity, and education, were almost 11 times as great in HIV+ as in HIV− individuals (adjusted odds ratio (aOR) = 10.97, 95% CI = 6.37–18.88) when all person-visits were analyzed. The odds were lower, but remained significant, when weight loss, which had a strong association with HIV before cART, was removed as a FRP criterion (OR = 4.49, 95% CI = 1.98–10.09). After the establishment of cART, one study (for MACS) demonstrated a significantly higher frailty prevalence in HIV+ (12%) than HIV− men (9%) ($P = .002$).[16] Further support for an association with HIV status was provided in the ALIVE cohort, in which HIV was associated with a 66% greater likelihood of frailty (aOR = 1.66, 95% CI = 1.24–2.21)[15] and in a study from South Africa in which the odds of frailty in those with HIV were more than twice as great (aOR = 2.14, 95% CI = 1.16–3.92).[21]

Age

In the pre-cART MACS, a 10-year increase in age was associated with a significantly greater risk of frailty (OR = 1.61, 95% CI = 1.21–2.15), which was lower but remained significant when AIDS was excluded (OR = 1.53, 95% CI = 1.11–2.11).[24] This persisted in the cART era (1996–2005), with a 10-year age increase associated with a greater risk of frailty (OR = 1.52, 95% CI = 1.24–1.87).[25] In later MACS data from 2007 to 2011, the proportion of visits at which frailty was demonstrated increased with increasing age.[16] Age was significantly associated with frailty in two additional studies.[15,20] In a South African study, older age was a significant predictor in HIV+ women but not men (OR = 2.50, 95% CI = 1.35–4.58) in a predominantly female HIV+ cohort (73.1%).[21] Another study showed no association with age and frailty after controlling for CD4 count, but older age was significantly associated with lower CD4 count, which predicted frailty.[19]

Sociodemographic Factors

Studies varied in sociodemographic factors presented. In early MACS analysis, before 1996,[24] college education was associated with greater frailty, but after 1996, the converse is seen, with lower educational attainment associated with greater frailty (OR = 1.73, 95% CI = 1.19–2.50)[25] and conversion to frailty.[16] Some studies[20] support this association between frailty and lower educational achievement but not others. Ethnicity (non-Hispanic black) was associated with frailty in the MACS cohort only after 1996.[16,25] Unemployment and low annual income were significantly associated with frailty in two studies[18,20] but not reported elsewhere.

Comorbid Conditions

The recording and handling of comorbidities varied between studies, with no standardized list used. Comorbidities were ascertained from a combination of self-report, laboratory parameters, and clinical notes review. Studies reported on specific comorbidities or comorbidity counts.[15,18–21] In studies in which comorbidities were examined, individuals with HIV who were frail had significantly more comorbidities than those who were robust.[15,16,18,20] The most consistently replicated comorbidities included psychiatric disease, particularly moderate to severe depression;[16,18,20,25] cognitive impairment;[20] chronic kidney disease;[16,20] diabetes mellitus;[16] and low body mass index.[20,21] Hepatitis C co-infection was associated with frailty in only one study and was restricted to those aged 50 and older.[19]

HIV Factors

$CD4^+$ Cell Count

Low $CD4^+$ count was the most consistently reported HIV factor associated with frailty, with current $CD4^+$[14–16,18,21,24,25] more predictive than nadir count, which showed significant association in only one study.[20] In MACS, median $CD4^+$ count increased over the duration of the study, with a corresponding drop in frailty prevalence overall, although the risk of frailty increased as $CD4^+$ fell ($CD4^+$ count 100 cells/μL: aOR = 2.80, 95% CI = 1.97–3.98; $CD4^+$ count 200 cells/μL: aOR = 1.98, 95% CI = 1.57–2.50; $CD4^+$ count 350 cells/μL: aOR = 1.36, 945% CI = 1.22–1.50).[25] This $CD4^+$ relationship was also observed in one cross-sectional study, with frailty prevalence of 43.5% for $CD4^+$ of less than 200 cells/μL, 19.2% for 200 to 350 cells/μL, and 7.8% for more than 350 cells/μL.[19] A high $CD4^+$ count was protective of frailty in one study, with a $CD4^+$ count of greater than 750 cells/μL associated 33% lower odds of frailty (OR = 0.66, 95% CI = 0.57–076).[25] $CD4^+$ count remained a strong predictor of frailty even in individuals with viral suppression and when AIDS and comorbidities such as tuberculosis and hepatitis C were controlled for.[21,25]

Viral Load

Viral load (VL) is not as strongly associated with frailty as $CD4^+$ count, with positive association observed only in pre-cART MACS, with the odds of those with a VL of more than 50,000 copies/mL having FRP being almost

three times as great (OR = 2.91, 95% CI = 1.08–7.85) as that of those without.[24] Frailty remained more common in those with a VL of more than 50,000 in the post-cART era but not significantly so after adjusting for CD4 count.[25] Other studies report no significant association with peak or current VL or virological failure on treatment.[15,18,19,21]

AIDS

When the relationship between AIDS (not including $CD4^+$ <200 cells/μL) and frailty was examined, all but one study[18] showed the risk of frailty to be higher in those with AIDS. In MACS, risk was lower after the introduction of cART (before cART: OR = 9.89, 95% CI = 4.70–20.80; after cART: OR = 3.34, 95% CI = 2.24–4.94).[25] This association was less evident in a study of women, in which the greater risk of frailty was seen only in univariate (OR = 1.55, 95% CI = 1.03–2.34) and not multivariate analysis; when AIDS was excluded, frailty prevalence in those with HIV was 7%, compared with 8% in HIV− controls.[14] Last, individuals with AIDS were more likely to become frail than those without (OR = 1.57, 95% CI = 1.06–2.34).[16]

DISCUSSION

This systematic review found multiple studies that all demonstrated frailty in individuals with HIV. Frailty prevalence ranged from 5.0% to 28.6% depending on the cohort studied. Frailty in these studies was associated with older age but was present at younger ages not traditionally associated with frailty, which is mainly seen as a syndrome of old age. HIV increased the likelihood of developing frailty, and in individuals with HIV, older age, comorbidities, AIDS diagnosis, and low current and possibly nadir $CD4^+$ cell count were predictors of frailty.

To the knowledge of the authors, this is the first evaluation of frailty in individuals with HIV using systematic review methodology. The strengths of this study include a comprehensive search strategy encompassing multiple electronic databases alongside conference proceedings and target journals in an attempt to capture all of the published literature. In addition, the focus on frailty assessment based upon the Fried FP attempted standardization across the studies. Although heterogeneity was still considerable, inclusion of alternative frailty assessment methods would have increased heterogeneity. Despite recent international attempts, there is still no consensus definition of frailty[12,28] although the FP is the most commonly used tool in population-based studies.[13]

To contextualize the prevalence of frailty in individuals with HIV, studies in HIV− populations using the FP in community-dwelling adults aged 65 and older include the U.S. Cardiovascular Health Study, in which the prevalence was 6.9%,[9] and a 2012 systematic review of 15 studies (n = 44,894), in which the prevalence was 9.9%.[29] The Study of Health, Aging and Retirement in Europe, which included a younger cohort, found a prevalence of 4.1% in individuals aged 50–64 and 17.1% in those aged 65 and older.[30] Therefore, the prevalence seen in the broadly younger HIV+ population, with a highest median age of 57, is comparable with that of cohorts of HIV− individuals aged 65 and older.

There are some limitations to this review. First, despite a thorough search strategy, some articles may have been missed. This would be important if these contradicted the results presented here, but given the global finding of frailty occurrence and chiefly consistent associated factors, it is likely that the effect would be small. Second, the large amount of heterogeneity across the studies in terms of the populations studied and the interpretation of the FP make comparisons difficult. Third, transitions between frailty states were not evaluable in the cross-sectional studies and, where measured in longitudinal studies, showed movement in and out of frailty, which makes defining its occurrence difficult. Last, some of the data presented come from the era before effective ART and so may not reflect the current largely well-treated cohort, who may have a different aging trajectory from that of those diagnosed before its availability.

The study populations were heterogenous, particularly the longitudinal cohorts, which focus on particular populations, including men who have sex with men in MACS,[16,24] intravenous drug use in ALIVE,[31] and women in the Women's Interagency Health Study.[14] Most studies originated from the United States, suggesting a need to explore geographical differences in frailty and the many potential confounders such as nutrition, late versus early diagnosis, HIV duration, and ART experience. The majority of studies used convenience rather than random sampling strategies, making it difficult to determine the role of selection bias and confounding. Furthermore, most recruited through HIV clinics. Clinic attendees may represent the less-healthy end of the spectrum of service users and therefore bias the study toward overestimation of frailty; conversely, individuals at the fitter end of the cohort may be more able to attend or be more proactive about their own health, leading to underestimation.

With regard to the interpretation of the FP, the vast majority used a FRP based on retrospective data or a modified FP, none of which, including the original phenotype, have been validated in younger HIV+ cohorts, which may affect the accuracy of frailty diagnosis, with potential for misclassification. In MACS particularly, frailty may have been underestimated when four rather than five criteria were used, because a trend of reducing frailty prevalence was reversed with the addition of grip strength in 2005.[16] Despite this lack of validation, when the predictive ability of the phenotype in terms of adverse outcomes was examined, it appeared to be consistent with that of traditional elderly cohorts.[15,20,26] Using population-based cut-offs for phenotypic criteria has been shown to correlate well with original methodology.[32]

A question remains as to whether there is equivalence between frailty in younger HIV+ individuals and older HIV− individuals. There are some similarities in that prevalence appears to increase with age and pathophysiological mechanisms may overlap. Recent attention has fallen on the role of inflammation as a driver of or trigger for frailty states through multisystem degradation.[11,33] Inflammatory profiles appear similar in those with and without HIV.[34,35] Early immune insult and sustained proinflammatory environment may trigger the premature occurrence of

frailty in HIV, which could explain why current immune dysfunction, evidenced by lower CD4 cell counts, is demonstrated as a consistent predictor of frailty in HIV.

The FP is criticized for using a one-dimensional approach to frailty that focuses too heavily on physical characteristics,[36] which in a HIV context may disproportionately represent those with lipodystrophy secondary to certain ART, although this and other markers of body composition and sarcopenia have not been widely explored as explanatory factors. Self-reported surrogate markers of exhaustion and low physical activity may also be overreported in individuals with additional comorbid conditions, particularly depression, which may be a confounding factor. It cannot be said that frailty is associated with the same negative outcomes of frailty as seen in older adults because longitudinal work reporting this is limited.

Before making any recommendations regarding routine assessment and treatment of frailty in individuals with HIV, alternative explanations, particularly the role of unrecognized depression, needs to be considered. Given the link between immune dysfunction and low $CD4^+$, it may be reasonable to investigate the role of ART in ameliorating frailty in those naïve to treatment or with poor adherence, particularly in light of results of the Strategic Timing of AntiRetroviral Treatment trial, which promotes early initiation of ART, avoiding low $CD4^+$ counts.[37] This should accompany wider public health approaches to proactive testing to avoid late diagnosis and advanced immunosuppression. Given the potential adverse outcomes associated with frailty, certain predictors may prompt targeted frailty assessment and, where found, trigger intervention, which should revolve around multidisciplinary comprehensive geriatric assessment. It would seem a reasonable approach to recommend positive lifestyle interventions, particularly exercise, which may have wider-reaching benefits for the cohort as a whole.

This review highlights the question of frailty in individuals with HIV, which appears to have prevalence comparable with that of HIV− individuals aged 65 and older. Important predictors include older age, advanced immunosuppression, and comorbidities. There is an ongoing need for further research in the form of well-designed longitudinal cohort studies conducted across the life span in mixed populations that reflect the current cohort aging with HIV. Given the implications, the inclusion of frailty measures in established HIV longitudinal studies should continue, representing a vital source of information on incidence, pathophysiology, predictors of transition to higher frailty states, and outcomes of prefrailty and frailty. Although achieving a representative HIV− control group is challenging, studies with well-chosen controls will help to confirm any contribution of HIV in addition to other disease and sociodemographic factors to frailty. This and longitudinal work focusing on whether frailty in individuals with HIV is associated with the same adverse outcomes seen in HIV− individuals could promote clinical and research activity into prevention and reversal of frailty. Ultimately, HIV provides an ideal model to examine aging from mid- to late life, which may provide insights into frailty development in uninfected populations.

ACKNOWLEDGMENTS

Martin Fisher died while this final draft was in preparation.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper. Tom J. Levett received small grant funding for registrars awarded by the British HIV association in June 2014. Fiona V. Cresswell is a trustee and board member of Health Improvement Project Zanzibar.

Author Contributions: Levett: original project conception, methodology, literature search, review, data analysis, submitted and revised final draft, primary author. Cresswell: methodology, literature search, data extraction, review and comment on all drafts. Malik: methodology review, meta-analysis and statistics input, review and comment on all drafts. Fisher: project conception, consensus reviewer, review and editing of drafts of manuscript. Wright: project conception, methodology review, review, editing, commenting on all drafts.

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SUPPORTING INFORMATION

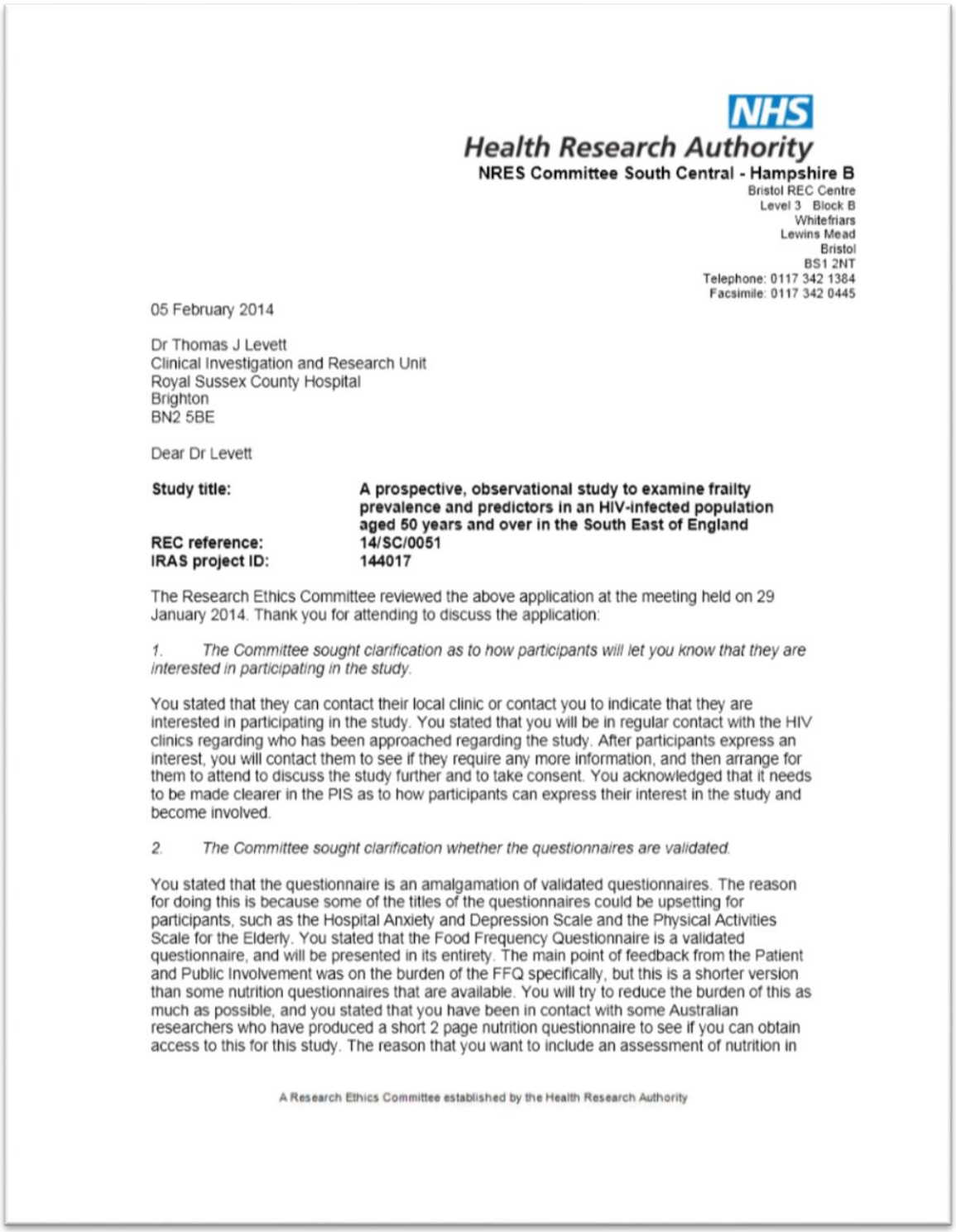
Additional Supporting Information may be found in the online version of this article:

Table S1. Table of comorbidities examined in each of the included studies

Please note: Wiley-Blackwell is not responsible for the content, accuracy, errors, or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

Appendix 2: Ethics Approvals Documents, Patient Information Sheets, Consent Forms

Figure A1-0.1: REC Approval with Conditions Letter 05-02-14 *(5 pages)*



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05 February 2014

Dr Thomas J Levett
Clinical Investigation and Research Unit
Royal Sussex County Hospital
Brighton
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Dear Dr Levett

Study title: **A prospective, observational study to examine frailty prevalence and predictors in an HIV-infected population aged 50 years and over in the South East of England**
REC reference: **14/SC/0051**
IRAS project ID: **144017**

The Research Ethics Committee reviewed the above application at the meeting held on 29 January 2014. Thank you for attending to discuss the application:

1. *The Committee sought clarification as to how participants will let you know that they are interested in participating in the study.*

You stated that they can contact their local clinic or contact you to indicate that they are interested in participating in the study. You stated that you will be in regular contact with the HIV clinics regarding who has been approached regarding the study. After participants express an interest, you will contact them to see if they require any more information, and then arrange for them to attend to discuss the study further and to take consent. You acknowledged that it needs to be made clearer in the PIS as to how participants can express their interest in the study and become involved.

2. *The Committee sought clarification whether the questionnaires are validated.*

You stated that the questionnaire is an amalgamation of validated questionnaires. The reason for doing this is because some of the titles of the questionnaires could be upsetting for participants, such as the Hospital Anxiety and Depression Scale and the Physical Activities Scale for the Elderly. You stated that the Food Frequency Questionnaire is a validated questionnaire, and will be presented in its entirety. The main point of feedback from the Patient and Public Involvement was on the burden of the FFQ specifically, but this is a shorter version than some nutrition questionnaires that are available. You will try to reduce the burden of this as much as possible, and you stated that you have been in contact with some Australian researchers who have produced a short 2 page nutrition questionnaire to see if you can obtain access to this for this study. The reason that you want to include an assessment of nutrition in

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this study is because nutrition is an overarching pathophysiology of frailty, and the impacts of poor nutrition are not known as yet.

3. The Committee queried whether the research team includes a nutritionist to analyse the results of the questionnaire.

You stated that a benefit of using this particular questionnaire as a measurement tool is that it comes with its own database that you can use to analyse the results, and the input of a nutritionist in the analysis is not required.

4. The Committee sought clarification of the funding for the study.

You stated that the funding stream stated in the application form is additional funding that you have applied for to assist with the laboratory costs of the supplementary blood sample study. The core funding for the study comes from your post as a clinical research fellow at the university.

5. The Committee queried whether there were other suitable cohorts globally and whether existing data may already be available.

You stated that, while there is a large elderly HIV population in San Francisco, previous research into frailty and HIV has actually come from different locations. For example, the discovery of the phenotype associated with frailty emerged from Boston. The difference between this study and previous research is that this study is restricted to patients over 50 and is aimed at making the research more clinically applicable. A mixture of measures and scales will be used to assess frailty, as currently, there are many different ways that it is measured. It is hoped that good predictors of frailty may emerge from this study and that this can then assist clinicians in identifying patients who need assistance over and above their standard HIV care.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Manager, Libby Watson, at: nrescommittee.southcentral-hampshireb@nhs.net

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

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Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

The Committee wishes to commend you on the excellent presentation of the study, both in the quality of the written documentation and also the presentation of the study by yourself at the Research Ethics Committee meeting.

1. The Committee requests that the PIS section 'Contacts for further information' is amended to detail how participants can express an interest in joining the study and what they need to do next. The Committee recommends that a detachable opt-in reply slip is appended to the PIS so that participants can provide their contact details and post it to the research team to indicate that they are interested in participating in the study.

2. The Committee requests that an item is added to the Consent Form to seek explicit consent for the researchers to access participants' medical records for the purposes of this study (which is separate to the access required by regulatory authorities currently stated in item 4 on the Consent Form).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for

medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering Letter		10 January 2014
Investigator CV	Tom Levett	10 January 2014
Investigator CV	Dr Juliet Wright	11 October 2013
Letter from Sponsor		09 December 2013
Other: UK CAB review		27 November 2013
Other: Dr. Winston review		11 December 2014
Other: Letter to GP	1.0	06 December 2013
Other: FOAL letter for physician	1.0	11 December 2013
Participant Consent Form: Supplimentry consent form for blood storage	1.0	12 December 2014
Participant Consent Form: FOAL consent form	1.0	28 November 2013
Participant Information Sheet: Frailty in Older Adults living with HIV	1.0	11 December 2013
Participant Information Sheet: PIS for blood sampling	1.0	12 December 2013
Protocol	1.0	11 December 2013
Questionnaire: FFQ EPIC Norfolk	validated	
Questionnaire: Study Questionnaire	validated	
REC application		10 January 2014

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

There were no declarations of interest.

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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/SC/0051	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

Professor Ron King
Chair
Email: nrescommittee.southcentral-hampshireb@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers" [SL-AR2]

Copy to: *Mr Scott Harfield*

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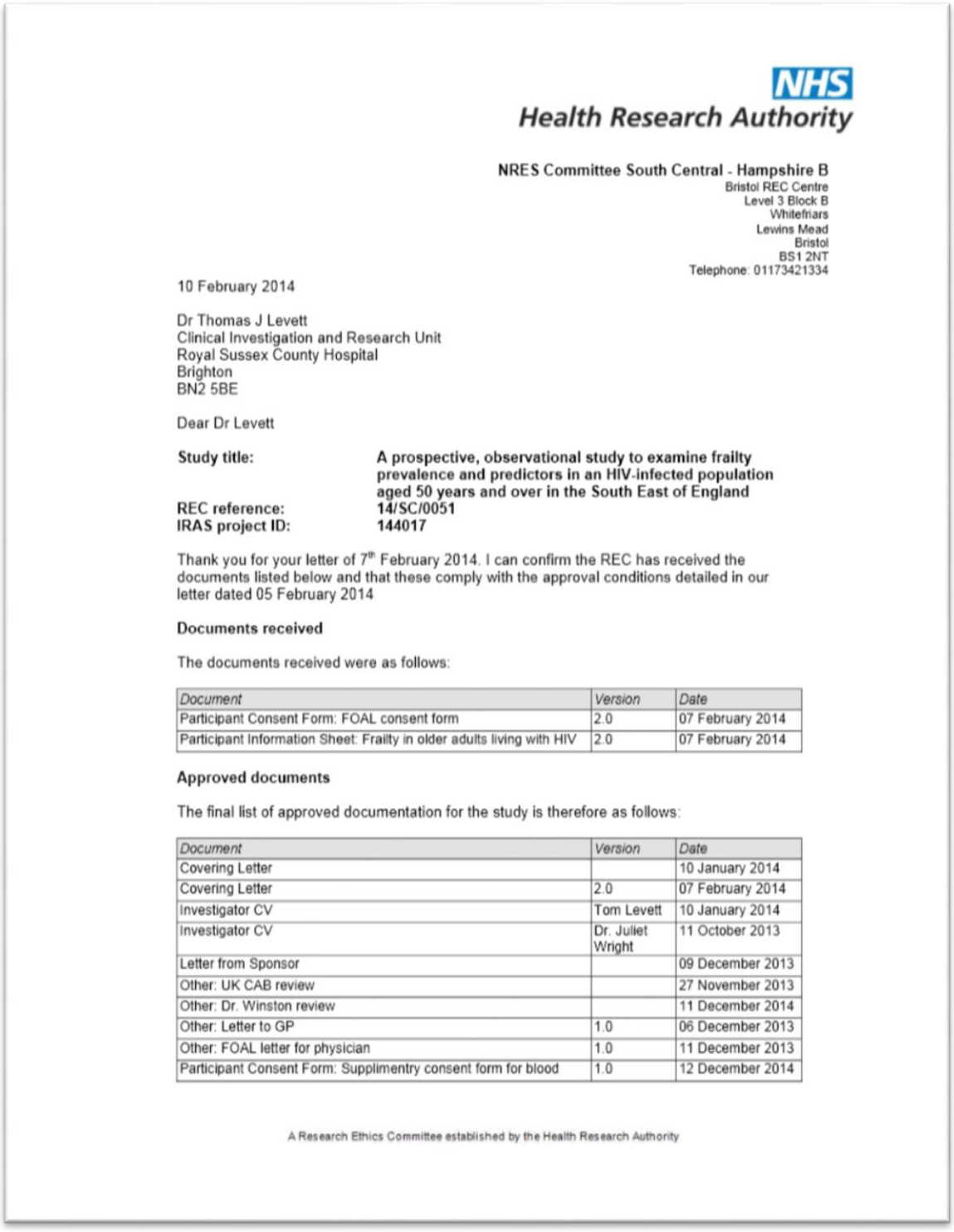
Figure A2-0.2: REC Approval Conditions Met Letter 10-02-14 *(2 pages)*



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10 February 2014

Dr Thomas J Levett
Clinical Investigation and Research Unit
Royal Sussex County Hospital
Brighton
BN2 5BE

Dear Dr Levett

Study title: **A prospective, observational study to examine frailty prevalence and predictors in an HIV-infected population aged 50 years and over in the South East of England**
REC reference: **14/SC/0051**
IRAS project ID: **144017**

Thank you for your letter of 7th February 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 05 February 2014

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Participant Consent Form: FOAL consent form	2.0	07 February 2014
Participant Information Sheet: Frailty in older adults living with HIV	2.0	07 February 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Covering Letter		10 January 2014
Covering Letter	2.0	07 February 2014
Investigator CV	Tom Levett	10 January 2014
Investigator CV	Dr. Juliet Wright	11 October 2013
Letter from Sponsor		09 December 2013
Other: UK CAB review		27 November 2013
Other: Dr. Winston review		11 December 2014
Other: Letter to GP	1.0	06 December 2013
Other: FOAL letter for physician	1.0	11 December 2013
Participant Consent Form: Supplimentry consent form for blood	1.0	12 December 2014

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storage		
Participant Consent Form: FOAL consent form	2.0	07 February 2014
Participant Information Sheet: PIS for blood sampling	1.0	12 December 2013
Participant Information Sheet: Frailty in older adults living with HIV	2.0	07 February 2014
Protocol	1.0	11 December 2013
Questionnaire: FFQ EPIC Norfolk	validated	
Questionnaire: Study Questionnaire	validated	
REC application		10 January 2014

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/SC/0051 **Please quote this number on all correspondence**

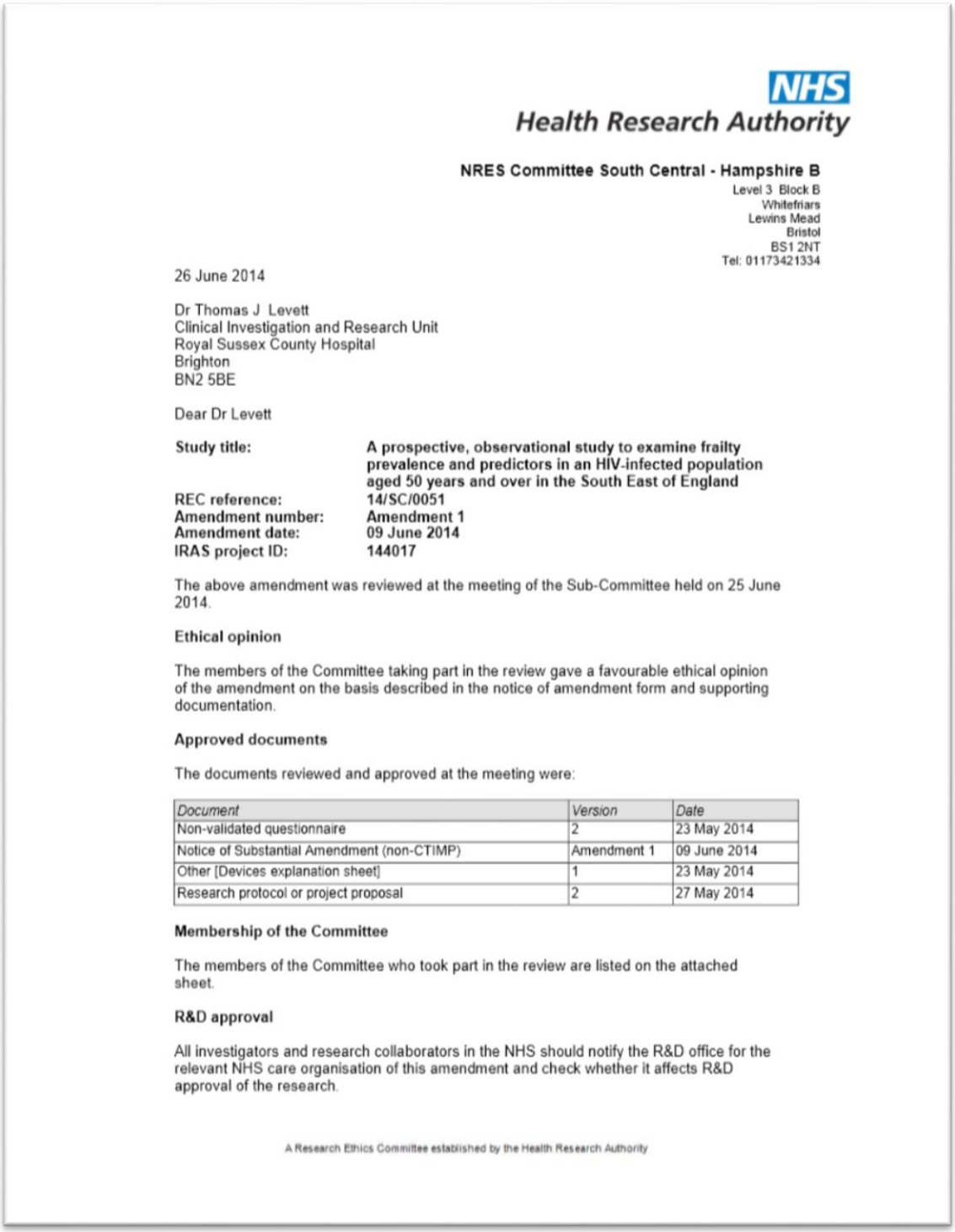
Yours sincerely

Miss Natasha Bridgeman
REC Assistant

E-mail: nrescommittee.southcentral-hampshireb@nhs.net

Copy to: *Mr Scott Harfield,*
Mr Scott Harfield, Brighton and Sussex University Hospitals NHS Trust

Figure A2-0.3: Substantial Amendment 1 REC Approval Letter 26-06-16 *(2 pages)*



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26 June 2014

Dr Thomas J Levett
Clinical Investigation and Research Unit
Royal Sussex County Hospital
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BN2 5BE

Dear Dr Levett

Study title:	**A prospective, observational study to examine frailty prevalence and predictors in an HIV-infected population aged 50 years and over in the South East of England**
REC reference:	**14/SC/0051**
Amendment number:	**Amendment 1**
Amendment date:	**09 June 2014**
IRAS project ID:	**144017**

The above amendment was reviewed at the meeting of the Sub-Committee held on 25 June 2014.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Non-validated questionnaire	2	23 May 2014
Notice of Substantial Amendment (non-CTIMP)	Amendment 1	09 June 2014
Other [Devices explanation sheet]	1	23 May 2014
Research protocol or project proposal	2	27 May 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

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Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/SC/0051:	**Please quote this number on all correspondence**

Yours sincerely

Professor Ron King (Chair)
Chair

E-mail: nrescommittee.southcentral-hampshireb@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Scott Harfield, Brighton and Sussex University Hospitals NHS Trust*

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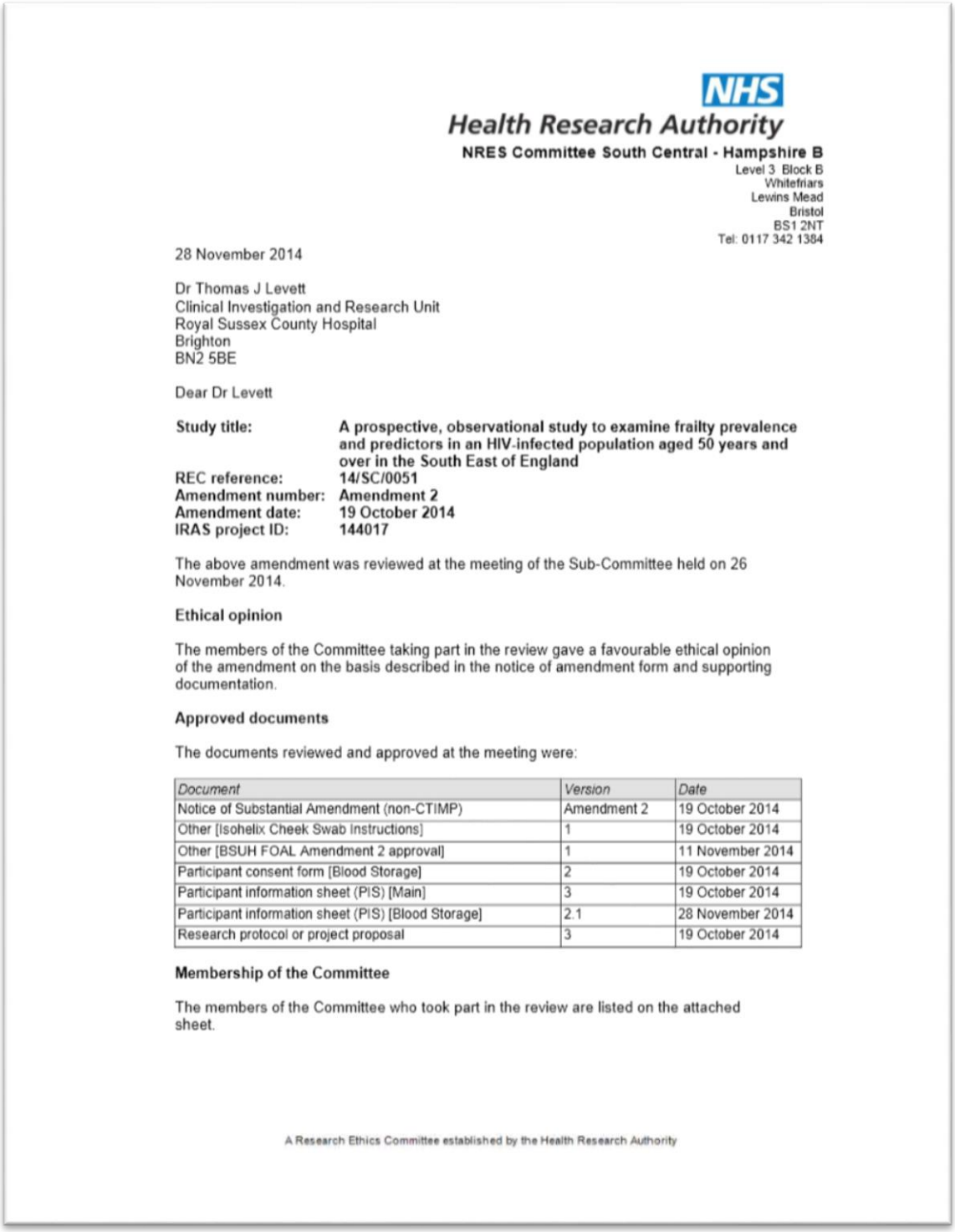
Figure A2-0.4: Substantial Amendment 1 REC Approval Letter 26-06-16 *(2 pages)*



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28 November 2014

Dr Thomas J Levett
Clinical Investigation and Research Unit
Royal Sussex County Hospital
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BN2 5BE

Dear Dr Levett

Study title: **A prospective, observational study to examine frailty prevalence and predictors in an HIV-infected population aged 50 years and over in the South East of England**
REC reference: **14/SC/0051**
Amendment number: **Amendment 2**
Amendment date: **19 October 2014**
IRAS project ID: **144017**

The above amendment was reviewed at the meeting of the Sub-Committee held on 26 November 2014.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Amendment 2	19 October 2014
Other [Isohelix Cheek Swab Instructions]	1	19 October 2014
Other [BSUH FOAL Amendment 2 approval]	1	11 November 2014
Participant consent form [Blood Storage]	2	19 October 2014
Participant information sheet (PIS) [Main]	3	19 October 2014
Participant information sheet (PIS) [Blood Storage]	2.1	28 November 2014
Research protocol or project proposal	3	19 October 2014

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Health Research Authority

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

14/SC/0051:	**Please quote this number on all correspondence**

Yours sincerely

Professor Ron King
Chair

E-mail: nrescommittee.southcentral-hampshireb@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mr Scott Harfield*

NRES Committee South Central - Hampshire B

Attendance at Sub-Committee of the REC meeting on 26 November 2014

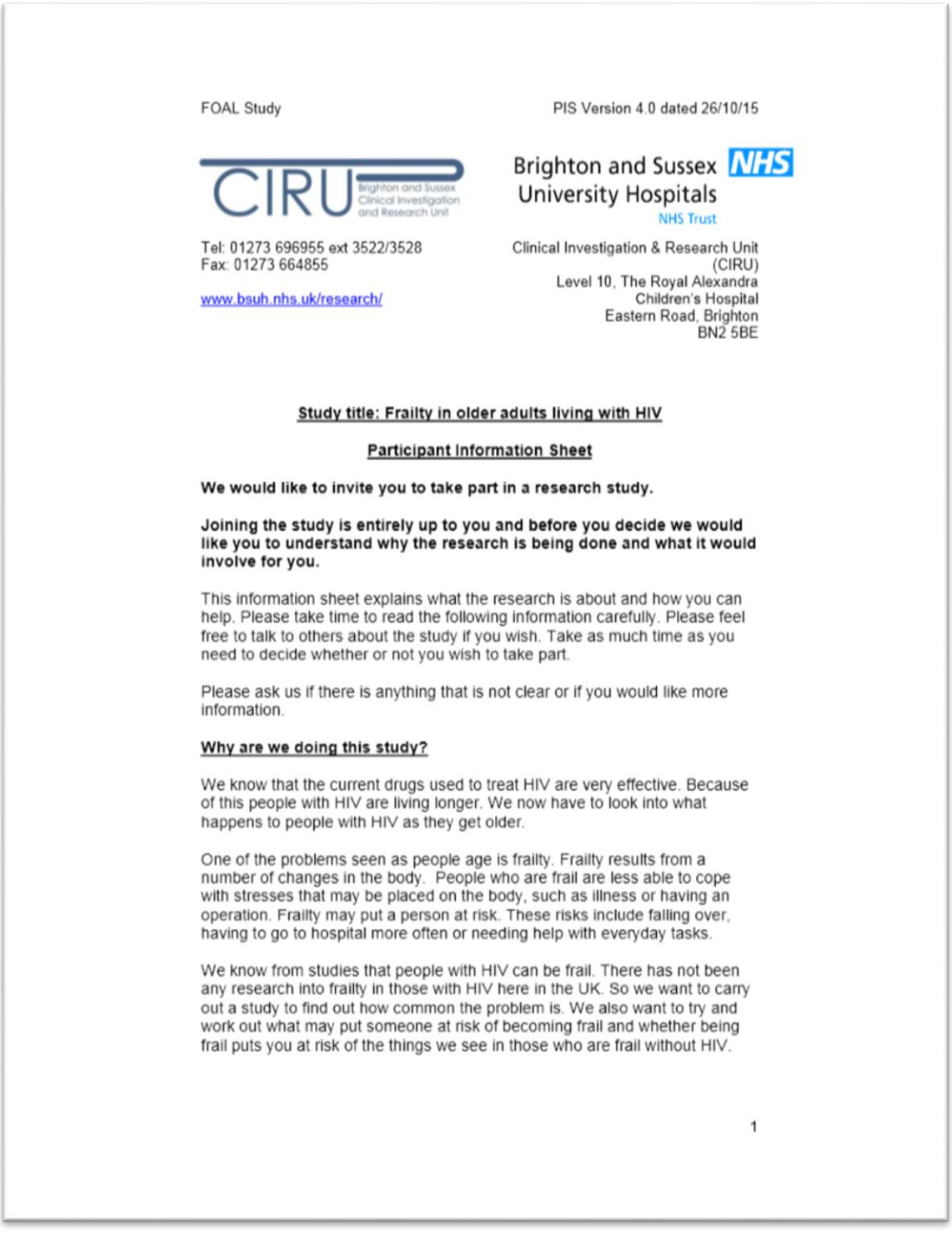
Committee Members:

Name	*Profession*	*Present*
Professor Ron King (Chair) – Chair	Mathematician (Retired)	Yes
Dr Chris Markham (Alternate Vice-Chair)	Associate Head of School (Research)	Yes

Also in attendance:

Name	*Position (or reason for attending)*
Miss Libby Watson	Research Ethics Committee Manager

Figure A2-5: Patient Information Sheet v4.0 26-10-15 *(7 pages)*



CIRU Brighton and Sussex Clinical Investigation and Research Unit

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Brighton and Sussex University Hospitals NHS Trust

Clinical Investigation & Research Unit (CIRU)
Level 10, The Royal Alexandra Children's Hospital
Eastern Road, Brighton
BN2 5BE

Study title: Frailty in older adults living with HIV

Participant Information Sheet

We would like to invite you to take part in a research study.

Joining the study is entirely up to you and before you decide we would like you to understand why the research is being done and what it would involve for you.

This information sheet explains what the research is about and how you can help. Please take time to read the following information carefully. Please feel free to talk to others about the study if you wish. Take as much time as you need to decide whether or not you wish to take part.

Please ask us if there is anything that is not clear or if you would like more information.

Why are we doing this study?

We know that the current drugs used to treat HIV are very effective. Because of this people with HIV are living longer. We now have to look into what happens to people with HIV as they get older.

One of the problems seen as people age is frailty. Frailty results from a number of changes in the body. People who are frail are less able to cope with stresses that may be placed on the body, such as illness or having an operation. Frailty may put a person at risk. These risks include falling over, having to go to hospital more often or needing help with everyday tasks.

We know from studies that people with HIV can be frail. There has not been any research into frailty in those with HIV here in the UK. So we want to carry out a study to find out how common the problem is. We also want to try and work out what may put someone at risk of becoming frail and whether being frail puts you at risk of the things we see in those who are frail without HIV.

Why have I been chosen to take part?

We have asked you to take part in his study as you have been diagnosed with HIV and are now aged 50 years or over. It was a doctor or nurse from your clinic who recognized that you could potentially be included in to our study.

Do I have to take part in this study?

It is up to you to decide if you want to take part in this study or not. It is completely voluntary. If you decide not to take part in this study the usual clinical care you receive will not be affected in any way.

If you decide to take part you are still free to stop your participation and withdraw from the study at any time and for any reason.

What will happen to me if I take part?

Your usual treatment of both your HIV and any other medical conditions will not change.

If you decide to take part in this study we will ask you to attend an initial assessment. We plan to carry out these assessments in the Clinical Investigation and Research Unit (CIRU) in the Royal Sussex County Hospital in Brighton (map and directions included), or in your usual HIV clinic if outside of Brighton.

We expect the first visit to take approximately 2 hours.

At the visit you will be seen by the study doctor or a research nurse.
During this visit we will:

- Collect information from you about your lifestyle, personal and family medical history, the medications that you take and questions about your everyday function.
- Ask you to fill in some questionnaires that cover your background, ask about your diet and symptoms such as pain and falls and look at your mood, memory and sense of well being.
- Measure your blood pressure.
- Perform a physical examination and take body measurements such as height, weight, waist size.
- Ask you to perform some short tests of grip strength and walking, these will help in testing for frailty.
- Ask you to complete some tests of memory and thinking.
- We will record your most recent blood tests. This may require us to take a fresh blood sample. We would take around 15mls (3 teaspoons).

We would also like to store a small amount 10mls (2 teaspoons) of your blood and perform a cheek swab so that we can use these samples in the future to look at blood and genetic markers of ageing. All samples are labelled with a study number and not your personal details. We have provided a separate information sheet about these samples and what we plan to do with them.

You do not have to agree to this part of the study if you would prefer not to. You can still take part if you say no to the blood and/or cheek swab tests.

Do I need to prepare for this visit?

There are no special things that you need to do before coming to the visit. We would be grateful if you could bring a current list of your medicines to the visit. During the visit we will be doing some tests of memory and simple brain function such as reaction time and listing words. Some of these are on computer but you do not need any special computer skills. If you wear glasses for reading then you should bring these along.

Alcohol could effect how well you perform in these tests, giving us a false impression. We recommend that you should not consume alcohol for at least 24hours before the visit.

Will this be my only visit?

No, some people will have a DEXA (Dual-energy X-ray absorptiometry) scan. After your first visit we will also telephone you at 6 months to ask you a small number of questions to see if you have been into hospital, fallen over or have had any change in how you manage day to day tasks since we last had contact with you. This call should take no longer than 10 minutes. We would then like to see you again in person one year after your first visit. There would be no more visits after this but we will phone you one last time around September 2016, just before the study finishes.

What will happen on the follow-up visit after one year?

On the follow up visit we will update any changes or additions to the information you gave us at visit one. We will ask you to repeat our questionnaire and memory tests and we will repeat the same examination as visit one.

What is a DEXA and who will get one?

A DEXA scan is a type of X-ray that is useful for looking at the way your body is made up. It gives us information on muscles and bones. It is a quick and painless test that is performed with you lying down on a scanning table in loose clothing. DEXA scans will be carried out in CIRU in Brighton.

Not everyone will receive a DEXA. We will scan those people who based on our assessment fall into the frail category and a selection of people of the same age and gender who are not frail, to compare the difference.

Is any medication being used in this study?

No, this is an observational study so it does not require you to take any specific study medications. Your usual treatment for HIV and any other medical conditions will not be affected in any way.

How long will the study go on for?

The study will finish in October 2016, so the longest you can be in the study is just over 2 years.

What happens when the study is finished?

You will continue to attend your normal clinic appointments as you will do throughout the study.

What are the possible benefits of joining this study?

There are no direct benefits in taking part in this study. However, the study will answer some important questions, which may help guide the way we manage your HIV in the future. This may include development of the service provided to older adults with HIV both locally and further afield.

Will I be paid for taking part in this study?

You will not be paid to take part in this study but your travel expenses can be reimbursed.

What are the possible risks or disadvantages of taking part?

When a blood sample is taken you may experience minor discomfort and a bruise.

DEXA scans are a type of X-ray so should not be performed if there is any possibility that you could be pregnant. For women still having periods a pregnancy test will be offered before DEXA scanning. The amount of radiation received during a DEXA is trivial. The typical radiation received from this exposure is equivalent to approximately five hours of natural background radiation to which we are all subjected.

It is possible that by taking blood samples we may find an abnormal result. The majority of blood results will come directly from your HIV clinic and any extra tests are very much routine, so we do not expect to find new problems. Anything we do find will be passed on to your usual HIV doctor (and your GP if you wish). We can also inform you directly if you wish.

You will be encouraged to report anything that is troubling you to the research team.

Who will be told I am taking part in this study?

Your usual HIV doctor will be informed. We would also like to inform your GP, but we will only do this if you give us specific permission.

How is my information kept confidential?

Any contact details that we collect from you will be kept on a secure database. If you decide to join the study you will be given a study number. This study number will be used to identify the information we collect at the visits, not your name or any other identifying information. This way personal information and results are stored separately. Personal information will only be used to contact you to arrange appointments or carry out the telephone follow up.

We would like to review your medical notes during the study. All medical notes will be reviewed within your normal HIV clinic. No notes will leave the clinic or be shared with anyone else not involved in the study. If you join the study your notes may also be looked at by representatives of the study sponsor (Brighton and Sussex University Hospitals NHS Trust-BSUH) or the regulatory authority to check that the study is being carried out correctly.

All records that identify you will be kept confidentially and will not be made available to the public. If results of this study are published your identity will remain confidential.

Data collected will be kept for 10 years after the end of the study. It will then be disposed of securely.

It may be useful to repeat this kind of study in the future to see what has happened over a period of time. To allow us to do this we would like to store your contact details after the study has finished. This would allow us to contact you to see if you would be interested in any future studies. It is perfectly fine if you would prefer not to do this. Saying no will not affect you taking part in this study and will mean that your personal details will be removed at the end of the study period.

What happens if I want to leave the study?

If you join the study you are free to leave the study at any point and for whatever reason. Leaving the study will not affect their care you receive from your usual HIV team. If you have already seen us and provided information and/or blood for our study, we would plan to keep the information/blood that we already have. But, we would delete your personal details and not collect any further information from you. If you would prefer all anonymous information to be deleted and blood to be disposed of, then please let us know.

Though highly unlikely, if for some reason during this study you are no longer able to make decisions for yourself we will not collect any more information from you. The information we already have will be kept in the same way as mentioned above.

What happens with the results of this study?

Your identity will not appear in any report or publication. Once completed, the results of this study will be analysed and published in a medical journal for

scientific purposes. We are happy to share with you the results of this study if you would like.

Who is organising and paying for this research?

The research is being organised through Brighton and Sussex University Hospitals NHS trust, who are the sponsor for this study. Funding has been provided by the Clinical Investigation and Research Unit, through Brighton and Sussex Medical School.

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect the interests of the research participants. This study has been reviewed and given a favourable opinion by the Hampshire-B Research Ethics Committee on the 10th February 2014.

What happens if there is a problem?

BSUH hold insurance policies which apply to this study.

If you wish to complain of have any concerns about any aspect of the way you have been treated during the course of this study you should immediately inform Dr. Tom Levett on 01273 696955 ext 7044 or The HIV research team on 01273 523079

The normal NHS complaints procedures are also available to you. The Patient Advice and Liaison Service (PALS) can be contacted on 01273 696955 ext 4029 or via email at complaints@bsuh.nhs.uk

What should I do if I would like to take part?:

If you would like to take part in the study, you can let us know through either of the ways listed below:

1. Return the attached reply slip at the end of this information sheet.
2. Send us an email with you name and contact telephone number to our dedicated research email address ejcresearch@bsuh.nhs.uk with subject heading 'FOAL study'.

Contacts for further Information:

If you have any questions about this research please feel free to ask:

Dr Tom Levett, Clinical Research Fellow CIRU, Royal Sussex County Hospital
Eastern Road
Brighton
Tel: 01273 696955 Ext 7044
Email: tom.levett@bsuh.nhs.uk

FOAL- Frailty study reply slip:

If you would be interested in finding out more information about, or taking part in the FOAL frailty study, please fill in your contact details below and return this form in the supplied pre-paid envelope to:

Dr. Tom Levett
Clinical Investigation and Research Unit (CIRU)
Level 5,
The Royal Sussex County Hospital,
Eastern Road
Brighton
BN2 5BE

Contact details:

Name: _____

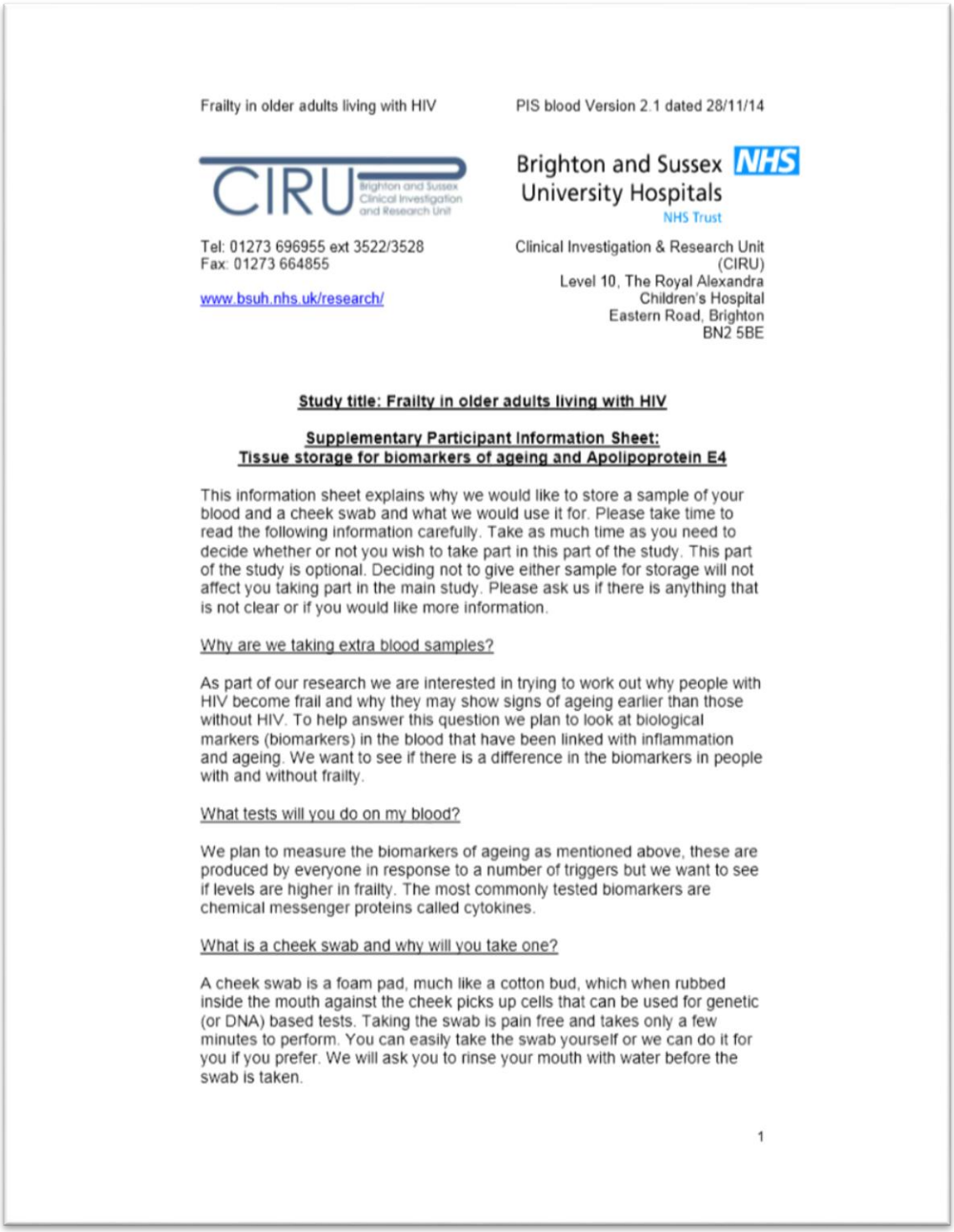
Contact telephone no. _____

Contact email address (if preferable):

_____

Alternatively, you can email us at ejcresearch@bsuh.nhs.uk with the subject heading 'FOAL study'.

Figure A2-6: Supplementary Patient Information Sheet v2.1 28-11-14 *(2 pages)*



CIRU Brighton and Sussex Clinical Investigation and Research Unit

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Fax: 01273 664855

www.bsuh.nhs.uk/research/

Brighton and Sussex University Hospitals NHS Trust

Clinical Investigation & Research Unit (CIRU)
Level 10, The Royal Alexandra Children's Hospital
Eastern Road, Brighton
BN2 5BE

Study title: Frailty in older adults living with HIV

Supplementary Participant Information Sheet:
Tissue storage for biomarkers of ageing and Apolipoprotein E4

This information sheet explains why we would like to store a sample of your blood and a cheek swab and what we would use it for. Please take time to read the following information carefully. Take as much time as you need to decide whether or not you wish to take part in this part of the study. This part of the study is optional. Deciding not to give either sample for storage will not affect you taking part in the main study. Please ask us if there is anything that is not clear or if you would like more information.

Why are we taking extra blood samples?

As part of our research we are interested in trying to work out why people with HIV become frail and why they may show signs of ageing earlier than those without HIV. To help answer this question we plan to look at biological markers (biomarkers) in the blood that have been linked with inflammation and ageing. We want to see if there is a difference in the biomarkers in people with and without frailty.

What tests will you do on my blood?

We plan to measure the biomarkers of ageing as mentioned above, these are produced by everyone in response to a number of triggers but we want to see if levels are higher in frailty. The most commonly tested biomarkers are chemical messenger proteins called cytokines.

What is a cheek swab and why will you take one?

A cheek swab is a foam pad, much like a cotton bud, which when rubbed inside the mouth against the cheek picks up cells that can be used for genetic (or DNA) based tests. Taking the swab is pain free and takes only a few minutes to perform. You can easily take the swab yourself or we can do it for you if you prefer. We will ask you to rinse your mouth with water before the swab is taken.

This swab will be used to test for a specific gene called apolipoprotein E4 (APO-E4). A gene is a small section of your genetic make-up, your DNA, which provides the instructions needed to make a protein. We are interested in this gene as it is a marker of brain function in ageing and the E4 version of it may be a risk factor for developing memory problems later in life. So we want to see how people with and without the gene compare in terms of frailty and how they perform on memory tests. No other genes or substances will be tested on this sample

How will the samples be stored?

Your samples will be labelled with your study number only, so it will be anonymous to any laboratory staff. The samples will be frozen until the study is full and then we will analyse them. After the analysis has been carried out we will safely dispose of all samples. We do not plan to keep any samples after the study has finished.

What happens to my samples if I choose to leave the study?

That is up to you. We would naturally like to analyse the samples but if you prefer all samples that you have provided will be destroyed.

Can I find out the result of these tests?

We plan to keep all samples anonymous and analyse them without your personal details. This means we would not be able to identify your individual test result. So we will not be able to tell you the result of these tests.

Do I have to agree to give blood for these tests?

No you do not. Deciding that you would rather not give a blood test for the biomarkers and/or the cheek swab for the APO-E4 gene test will not affect you taking part in the main study and will not affect your usual treatment in anyway.

Contacts for further Information:

If you have any questions about the information provided in this sheet please feel free to ask:

Dr Tom Levett
Clinical Research Fellow

CIRU
Royal Sussex County Hospital
Eastern Road
Brighton
Tel: 01273 696955 Ext 7044
Email: tom.levett@bsuh.nhs.uk

Figure A2-7: Consent Form v2.0 07-02-14 *(2 pages)*

CIRU Brighton and Sussex Clinical Investigation and Research Unit

Brighton and Sussex University Hospitals NHS Trust

Tel: 01273 696955 ext 3522/3528
Fax:01273 664855
www.bsuh.nhs.uk/research/

Clinical Investigation & Research Unit (CIRU)
Level 10, The Royal Alexandra Children's Hospital
Eastern Road, Brighton
BN2 5BE

Consent Form

Study title: **Frailty in older adults living with HIV**
Study No:
Patient ID number for this study:
Name of Researcher: Dr Tom Levett

	Please initial box if you agree:
1. I confirm that I have read and understand the information sheet for the above study dated *07/02/14 version 2.0*. I have had the opportunity to consider the information and ask questions and these have been answered to my satisfaction.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason and without my medical care or legal rights being affected.	
3. I understand that my identity will never be disclosed and any information collected will remain confidential.	
4. I understand that relevant sections of my medical notes will be reviewed and may be used as a source of information by the study investigators. I give permission for my notes to be used for this purpose.	
5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the regulatory authorities or the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
6. I agree to take part in the above study.	

Consent Form- page 2 of 2

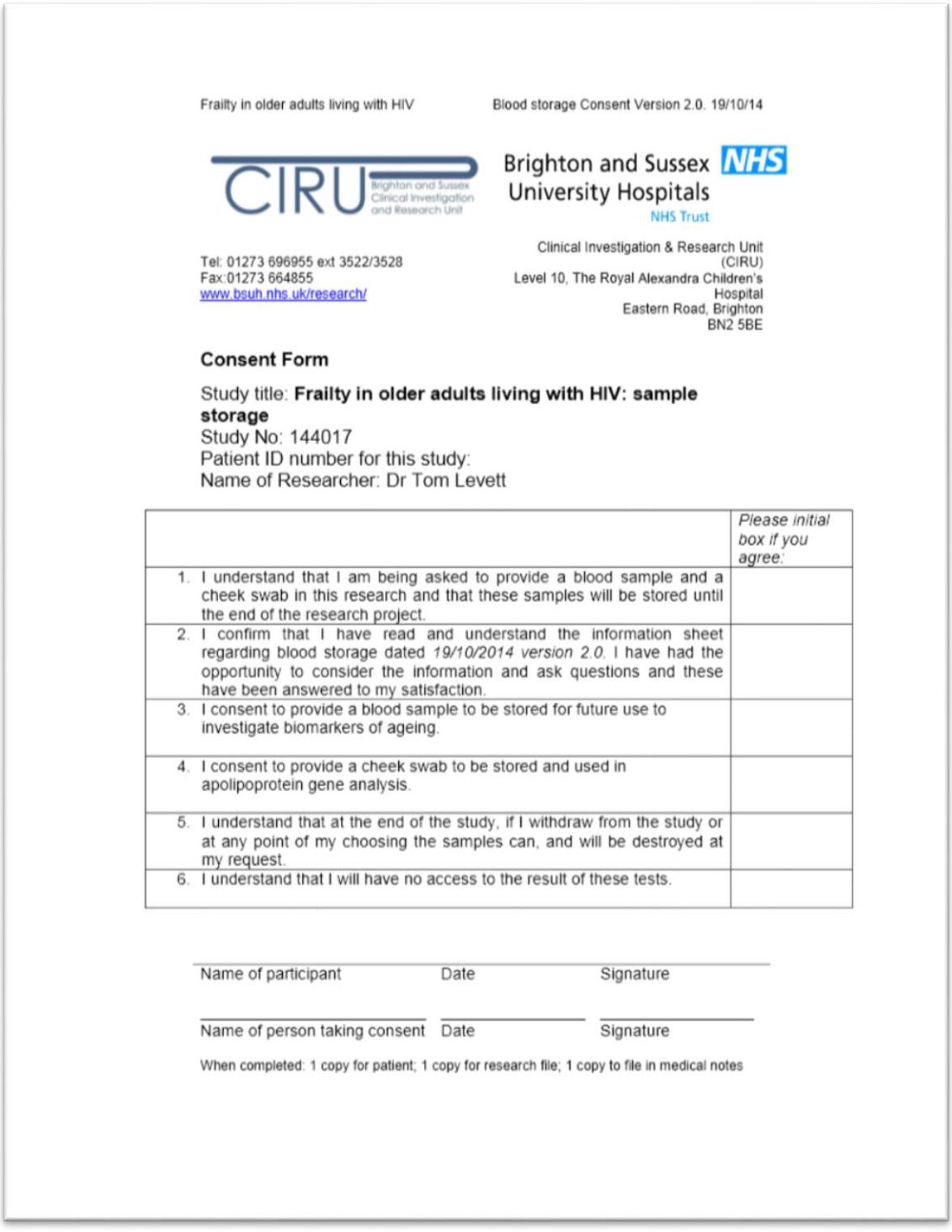
Study title: **Frailty in older adults living with HIV**
Study No:
Patient ID number for this study:
Name of Researcher: Dr Tom Levett

Not providing consent for the items listed below will not affect you taking part in the study and we assure you that they will not happen. Please initial the box if you ARE happy for the study team to do the item listed.	*Please initial box if you agree:*
7. I agree to my GP being informed of my participation in this study.	
8. I understand that my contact details will be stored securely and may be used to contact me in the future about new research studies.	
9. At the end of the study I would like to receive a summary of the overall study results.	

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Name of person receiving consent	Date	Signature

When completed: 1 copy for patient; 1 copy for research file; 1 copy to file in medical notes

Figure A2-8 - Blood Storage Consent Form v2.0 19-10-14 *(1 page)*



Brighton and Sussex University Hospitals NHS Trust

Tel: 01273 696955 ext 3522/3528
Fax:01273 664855
www.bsuh.nhs.uk/research/

Clinical Investigation & Research Unit (CIRU)
Level 10, The Royal Alexandra Children's Hospital
Eastern Road, Brighton
BN2 5BE

Consent Form

Study title: **Frailty in older adults living with HIV: sample storage**
Study No: 144017
Patient ID number for this study:
Name of Researcher: Dr Tom Levett

	Please initial box if you agree:
1. I understand that I am being asked to provide a blood sample and a cheek swab in this research and that these samples will be stored until the end of the research project.	
2. I confirm that I have read and understand the information sheet regarding blood storage dated *19/10/2014 version 2.0.* I have had the opportunity to consider the information and ask questions and these have been answered to my satisfaction.	
3. I consent to provide a blood sample to be stored for future use to investigate biomarkers of ageing.	
4. I consent to provide a cheek swab to be stored and used in apolipoprotein gene analysis.	
5. I understand that at the end of the study, if I withdraw from the study or at any point of my choosing the samples can, and will be destroyed at my request.	
6. I understand that I will have no access to the result of these tests.	

Name of participant Date Signature

Name of person taking consent Date Signature

When completed: 1 copy for patient; 1 copy for research file; 1 copy to file in medical notes

Appendix 3: Medical comorbidities examined in HIV and frailty studies

Study Chief author, year	Comorbidities investigated
Althoff, 2014[176]	Cancer at or within one year of visit CKD (eGFR <60ml/min/1.73m^2 body surface) Depression defined by Centres for Epidemiologic Studies Depression Scale (CES-D) score >16 Diabetes Mellitus (fasting glucose ≥126mg/dl or self-report with use of antidiabetic medications) Dyslipidaemia (based on laboratory parameters or self-report with use of lipid-lowering medications) Hepatitis C (detectable RNA in serum) Hypertension (SBP ≥140 and/or DBP≥90)
Desquilbet, 2007[166]	Cancer (based on medical notes review, timescale undefined) Neurological disorders (otherwise undefined)
Desquilbet, 2009[184]	Hepatitis B/C Depressive symptoms defined using CES-D Other comorbidities not examined as may be on causal pathway to frailty
Desquilbet, 2011[185]	Hepatitis C
Erlandson, 2012[178]	Comorbid conditions from problem lists, initial clinic intake history and clinic notes: Arthritis (osteo- and/or inflammatory arthritis) Cardiovascular disease (ischaemic, valvular, peripheral vascular, congestive heart failure) Chronic kidney disease (creatinine clearance <30ml/min) Chronic liver disease of other aetiology Diabetes Hypertension Lipoatrophy (self-reported)

Study Chief author, year	Comorbidities investigated
Erlandson, 2012 cont'd	Lung disease (COPD, asthma, pulmonary hypertension, interstitial lung disease)
	Malignancy (excluding non-malignant skin cancer)
	Neurological disease (seizure, dementia)
	Osteopenia or osteoporosis (T-score <-1.0 on bone density scan or prior stress fracture)
	Peripheral neuropathy
	Psychiatric disease (depression, anxiety, bipolar, schizophrenia, or otherwise not specified)
	Solid organ transplant
	Stroke or TIA
	Viral hepatitis (B, C or both)
Greene, 2015[4]	Comorbidities assessed using Charlson comorbidity index plus hepatitis C and peripheral neuropathy. Self-reported with notes verification
	Depression using the CES-D
Ianas, 2012[179]	Comorbidities derived from self-report and/or notes review:
	Coronary Artery Disease
	Diabetes Mellitus
	Dyslipidaemia
	Hepatitis B (prior measurement HBV DNA +/or HBsAg)
	Hepatitis C (ongoing viremia without treatment)
	Hypertension
	Lung Disease
	Neuropathy
	Psychological (depression, anxiety, bipolar, psychosis, personality disorder)
Onen, 2009[180]	Record comorbidities used with comorbidity defined as ≥2 of:
	Airways disease
	Cancer (AIDS and non-AIDS defining)

Study Chief author, year	Comorbidities investigated
Onen,	Cardiovascular disease (hypertension, CCF MI, stroke)
2009 cont'd [180]	Chronic viral hepatitis
	CKD Cognitive impairment (HIV dementia scale ≤10)
	Depression (Using Patient Health Questionnaire 9 (PHQ 9))
	Diabetes Mellitus
	Neuropsychiatric conditions (anxiety, bipolar, peripheral neuropathy)
Pathai,	Self-report +/or notes review. Comorbidity defined as ≥1 of:
2013[181]	Airways disease
	Cancer (AIDS and non-AIDS defining)
	Cardiovascular disease (MI, CVA)
	CKD
	Hypertension (SBP ≥140 and/or DBP≥90 or self-report and use of anti-hypertensives)
Piggott,	Self-reported comorbidity defined as >1 of:
2013[175]	Cardiovascular disease
	Cerebrovascular disease
	Chronic kidney disease
	Chronic lung disease
	Depressive symptoms using CES-D
	Diabetes
	Hypertension
	Liver disease
	Malignancy
Sandkovsky,	Medical records reviewed to give a count of comorbidities
2013[186]	Hepatitis C from medical records or serological tests
Terzain,	Active Hepatitis C based on serology
2009[174]	Depression as assessed by CES-D

Study Chief author, year	Comorbidities investigated
Davila-de la Llavre, 2013[182]	'chronic diseases' classed as: Cancer Diabetes Hypertension

Appendix 4: Supplementary data tables

Table A4.1: Uni- and multivariable analysis of the relationship between frailty and blood biomarkers.

		Association with frailty		
Variable	**Crude OR (95% CI)**	**aOR [a]**	**95% CI**	**p-value**
VACSI	1.03 (1.01-1.06)*	1.03	0.99-1.06	0.128
Haemoglobin	0.98 (0.96-1.00)	0.99	0.97-1.02	0.469
Anaemia	0.53 (0.18-1.60)	1.36	0.34-5.39	0.663
WCC	0.94 (0.80-1.11)	0.84	0.69-1.02	0.073
Neutrophils	0.96 (0.81-1.14)	0.84	0.64-1.09	0.196
Lymphocytes	0.82 (0.56-1.20)	0.67	0.41-1.08	0.101
Platelets	1.00 (0.99-1.00)	0.99	0.98-1.00	**0.013**
Albumin	0.92 (0.85-1.01)	0.95	0.87-1.03	0.231
ALT	1.00 (0.99-1.01)	1.00	0.98-1.01	0.627
AST (n=239)	1.02 (1.00-1.04)	1.01	0.99-1.03	0.253
ALP	1.00 (0.99-1.01)	1.00	0.99-1.01	0.481
Creatinine	0.99 (0.97-1.01)	0.99	0.97-1.00	0.137
GFR estimation	1.01 (0.99-1.03)	1.02	0.99-1.04	0.207
CMV positivity	1.45 (0.38-5.58)	2.23	0.49-10.17	0.301
High CMV IgG	3.28 (0.96-11.16)	2.85	0.69-11.69	0.146

[a] Adjusted for age, sex, HADS score and comorbidity count
* p<0.05; ** p<0.001

Appendix 5: Related Publications

Peer-reviewed publications:

Levett T, Cresswell F, Malik M, Fisher M and Wright J. A systematic review of frailty prevalence and predictors in HIV. Journal of the American Geriatrics Society. 2016 May;64(5):1006-14. doi: 10.1111/jgs.14101.

Abstracts:

Levett T, and Wright J. Sarcopenia in older adults with HIV and its association with frailty status. International Conference on Frailty and Sarcopenia Research, Barcelona. 2017.

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